Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.

Clinical Study Protocol: COU-AA-301

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
Study Number:	COU-AA-301
Study Phase:	3
Product Name:	Abiraterone acetate
IND Number:	71,023
EudraCT No:	2007-005837-13
Indication:	Treatment of Metastatic Castration-Resistant Prostate Cancer
Investigators:	Multicenter
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	Date	Version
Original Protocol:	February 7, 2008	1.0
Amended Protocol	July 30, 2008	2.0
	January 12, 2009	3.0
	August 26, 2010	4.0

Confidentiality Statement

PROTOCOL AMENDMENT 3.0

Following Interim Analysis, the Protocol is Amended to:

- Pursuant to the Independent Data Monitoring Committee (IDMC) recommendations on August 20, 2010, all patients will be unblinded and placebo patients will be offered treatment with abiraterone acetate.

SYNOPSIS

Sponsor:

Cougar Biotechnology, Inc

Name of Finished Product:
Abiraterone acetate

Name of Active Ingredient:

Abiraterone acetate

Study Title:
A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

Study Number:
COU-AA-301

Study Phase: 3

Primary Objective:

- To compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of which contains docetaxel

Secondary Objectives:

- To further evaluate the safety profile of abiraterone acetate plus prednisone
- To further characterize the pharmacokinetics (PK) of abiraterone acetate when administered concurrently with prednisone
- To further explore the potential utility of circulating tumor cells (CTCs) as a surrogate for clinical benefit
- To evaluate the impact of abiraterone acetate plus prednisone on health-related quality of life (QOL)

Study Design:

Multinational, multicenter, randomized, double-blind placebo-controlled study with a randomization allocation ratio of 2:1 between the abiraterone acetate group and the placebo group. Abiraterone acetate and placebo tablets will be referred to as study medication in a blinded fashion. Patients randomized to the abiraterone acetate group will receive a dose of 1000 mg daily (QD). Study medication will be administered as 4 x 250-mg abiraterone acetate tablets or 4 placebo tablets. Prednisone will be administered as 5 mg orally twice a day (bid) for both groups.

Randomization will be stratified according to the following:

- ECOG performance status: 0-1 versus 2
- Worst pain over the past 24 hours on BPI-SF: 0-3 (absent) versus 4-10 (present)
- 1 versus 2 prior chemotherapy regimens
- Type of progression: PSA only versus radiographic progression

Study Population:
Medically or surgically castrated male patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy.

Test Product, Dose, and Mode of Administration:
Abiraterone Acetate, 1000 mg/day (4 x 250-mg tablets) given orally

Duration of Treatment:
Informed consent may be obtained up to 30 days prior to Cycle 1 Day 1. Each cycle consists of 28 days. Patients will have a screening period of up to 14 days prior to randomization on Cycle 1 Day 1 and will be treated until disease progression.

Efficacy Assessments:
- Modified RECIST criteria will be used to assess tumor response and progression-free survival (PFS).
- Post-baseline PSA level will be used to measure prostate-specific antigen (PSA) response rate and time to PSA progression.
- Time to first skeletal-related events will be measured as the time to a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.
- The Brief Pain Inventory-Short Form (BPI-SF) and analgesic usage score will be used to measure the proportion of patients experiencing pain palliation and the time to pain progression.

Safety Assessments:
- Medical history, vital sign measurements, physical examination, and body weight
- Concomitant therapy and procedures
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Appendix 5)
- Blood chemistry, hematology, coagulation studies, serum lipids, and urinalysis
- Electrocardiograms (ECGs) and measurement of cardiac ejection fraction

Other Assessments
- Quality of Life (QOL) using Functional Assessment of Cancer Therapy-Prostate (FACT-P) Quality of Life questionnaire
- Fatigue evaluated by the Brief Fatigue Inventory (BFI) instrument
- Medical resource utilization (MRU) information
- PK measurements
- CTC enumeration

Statistical Methods

Sample Size:

The planned sample size of approximately 1158 patients (772 on abiraterone acetate and 386 on placebo) will provide 85% power to detect a difference between a median survival of 15 months in the abiraterone acetate group and a median survival of 12 months in the placebo group (hazard ratio=0.80) under the assumptions of a 2-tailed significance level of 0.05 and an enrollment of approximately 13 months over a total duration of approximately 30 months to obtain the required 797 total events.

One interim analysis and one final analysis are planned for the study using group sequential design. Detail of the design is provided in Section 9.

Efficacy Endpoints:

All randomized patients will be included in the intent-to-treat analysis (ITT) classified according to their assigned treatment group, regardless of the actual treatment received.

The primary efficacy endpoint is:

- Overall survival

Secondary efficacy endpoints are:

- Proportion of patients achieving a PSA decline ≥ 50% according to Prostate Specific Antigen Working Group (PSAWG) criteria
- Time-to-PSA progression based on PSAWG criteria
- Progression-free survival (PFS) based on imaging studies

Other Endpoints are:

- Proportion of patients with objective tumor response by modified RECIST (baseline lymph nodes size must be ≥ 2 cm to be considered a target lesion)
- Proportion of patients experiencing pain palliation using BPI-SF and analgesic score
- Time to pain progression
- Time to first skeletal-related event
- Modified PFS based on criteria for discontinuation of study treatment
- Proportion of patients achieving a decline in circulating tumor cells (CTCs)/7.5ml to less than 5.
- QOL total score and each subscale score as assessed by FACT-P

Distributions of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. The median times to event with two-sided 95% confidence intervals will be estimated. The stratified logrank test will be used as the primary analysis for treatment comparison; the estimates of the hazard ratios and their 95% confidence intervals will also be provided.

Response rate will be the proportion of patients fulfilling the respective criteria for

response. The relative risk (treatment: control) will be reported along with the associated 95% confidence interval. Statistical inference will be evaluated using Chi-square statistic; the Fisher's exact test may be used if the expected counts in some cells are small.

Sensitivity analysis for overall survival (OS) using non-stratified logrank test and cox proportional hazards model will also be performed as supportive analyses. Subgroup analyses will be carried out to assess if treatment effects are consistent within subgroup.

Safety Endpoints:

All patients who receive at least one dose of abiraterone acetate or placebo will be analyzed for safety. Safety summary will include adverse events, clinical laboratories parameters, and vital signs. Serious adverse events and deaths will be listed.

Interim and Final Analyses:

One interim analysis and one final analysis are planned after observing 534 and 797 death events, respectively. The cumulative alpha spent is 0.0124 and 0.0500 for the interim analysis and final analysis, respectively. All estimates will be adjusted in the context of group sequential testing design.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAWD	Antiandrogen withdrawal
ACTH	Adrenocorticotropic hormone
AD	Androgen deprivation
AE	Adverse event
AIPC	Androgen independent prostate cancer
ALT	Alanine aminotransferase (SGPT)
ALK-P	Alkaline phosphatase
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AR	Adverse reaction
BFI	Brief Fatigue Inventory
AST	Aspartate aminotransferase (SGOT)
bid	Twice daily
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German: Federal Institute for Drugs and Medical Devices)
BPI-SF	Brief Pain Inventory Short Form
BUN	Blood urea nitrogen
C	Celsius
CALGB	Cancer and Leukemia Group B
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
CBC	Complete blood count
CrCl	Creatinine clearance
CFR	Code of Federal Regulations
CIOMS	Council For International Organizations of Medical Sciences
CR	Complete Response
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRPC	Castration resistant prostate cancer

CRO	Contract research organization
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulphate
DRE	Digital Rectal Exam
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EP	European Pharmacopoeia
EU	European Union
F	Fahrenheit
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HEENT	Head, Eyes, Ears, Nose, Throat
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
HRPC	Hormone refractory prostate cancer
HTN	Hypertension
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LD	longest diameter
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LHRL	Luteinizing hormone releasing hormone
LN	Lymph Node
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MRU	Medical resource utilization
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NF	National Formulary Specifications
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PO	Per Os (by mouth)
PPI	Present pain index
PR	Partial Response
PROSQOLI	Prostate Cancer Specific Quality of Life Instrument
PT	Prothrombin time
PTT	Partial thromboplastin time

PK	Pharmacokinetics
PSA	Prostate Specific Antigen
PSAWG	Prostate Specific Antigen Working Group
QoL	Quality of life
RBC	Red blood cell (count)
RECIST	Response evaluation criteria in solid tumors
RH	Relative humidity
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SSRI(s)	Selective serotonin uptake inhibitor(s)
SUSAR	Suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
ULN	Upper limit of normal
US (A)	United States (of America)
USP	United States Pharmacopoeia
WBC	White blood cell (count)
WHO	World Health Organization

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1 INTRODUCTION

1.1 Metastatic Androgen-Independent Prostate Cancer

Prostate cancer has become an increasingly important health issue globally. With 679,060 men diagnosed each year, prostate cancers are the fifth most common tumor type worldwide [1]. It is estimated that in 2007, prostate cancer will be diagnosed in 218,890 men in the United States alone and that 27,050 will die [2].

The most significant morbidity of prostate cancer is bone metastasis. It develops initially in the axial skeleton and later in the appendicular skeleton [3] in advanced prostate cancer, and metastasis to bone is present in > 90% of patients [4]. These lesions cause pain, skeletal fractures, spinal cord compression, anemia and thrombocytopenia. Clinical sequelae include pain, paralysis, diminished mobility, fatigue and increased risk of infections. Side effects such as constipation and delirium from analgesics required to palliate pain are also significant. They further compromise patient quality of life.

In addition, soft tissue metastasis occurs in about 40% of advanced patients. Pelvic lymphadenopathy may lead to anatomic obstruction of the ureters, or fistula formation [4]. When tumor recurs in the prostate gland or bed, urethral obstruction may also ensue.

Prostate cancer is hormone sensitive at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation with medical [5] or surgical [6] castration, the median duration of disease control has been 13 to 22 months and overall survival 28-36 months [7]. The clinical status of patients after failure of castration is commonly referred to as hormone-refractory prostate cancer (HRPC), or androgen-independent prostate cancer (AIPC). However, recent investigations have established that tumor progression often remains androgen-dependent albeit at much reduced androgen levels after castration. Although used widely in clinical settings, the terms HRPC and AIPC do not reflect the biology of advanced prostate cancer where androgen receptor and its ligand remain pivotal in tumor growth. Prostate cancer progression after conventional medical or surgical castration should, therefore, be considered castration-refractory prostate cancer (CRPC).

In the castrate state, ligands to the androgen receptor are thought to be derived primarily from the adrenal glands. Conventional androgen deprivation therapy removes 90% of circulating androgens produced in the gonads. As much as 10% of circulating testosterone remains, in part due to the peripheral conversion of adrenal steroids to testosterone. In addition, several publications suggest that androgen levels in the microenvironment of prostate cancer may be maintained in spite of reduced systemic levels [8, 9]. The authors suggested that androgens might be sequestered by prostate tissue [9]. In patients with castrate levels of testosterone, the tissue levels of dehydroepiandrosterone, dihydrotestosterone, and androstenedione all remain sufficient to activate the androgen receptor (AR). Furthermore, the ARs are predominately located in the nucleus in biopsy tissue, indicating ligand-binding and the activation of androgen-dependent gene expression. Increased expression of the AR is common in advanced prostate cancer, and allows lower ligand levels to more strongly

activate the AR [10]. Another recent publication made the observation that in high risk primary prostate tumors and in metastatic biopsies, CYP17A1 gene expression is highly upregulated [11], suggesting the possibility of in situ production of androgens as autocrine or paracrine growth factors despite castration. Although these preliminary findings require further corroborating evidence, the need to suppress androgen production in adrenal glands and possibly at tissue levels persists in CRPC.

Complete androgen independence in CRPC is thought to be rare. A few patients (9%) have mutations in the androgen receptor [12], these changes could allow the androgen receptor to be activated by non-androgen ligands, or might allow ligand-independent AR association with coactivator molecules.

Patients with metastatic CRPC have a very limited life expectancy and most often die of their prostate cancer. The most important clinical features linked to survival of CRPC patients have been identified using multivariate analysis of long-term survival data in large patient cohorts [13, 14, 15]. Performance status, presence of pain, and hemoglobin levels emerged as the most important predictors of survival in CRPC patients who are candidates for chemotherapy.

Despite the improved survival observed in CRPC patients treated with docetaxel-based regimens, the median survival of patients receiving docetaxel chemotherapy was 17.5-18.9 months [16, 17]. Once the disease progresses after failing docetaxel-based therapy, there is no treatment that has proven to improve survival. Thus, new therapies are urgently needed.

1.2 Current Therapy for CRPC

Second line hormonal therapies in prostate cancer have limited efficacy, and none have received FDA approval. Historically, bilateral adrenalectomy was the first second line hormonal therapy to be evaluated [18]. Several of the adrenalectomized patients with widespread bone metastases had decreases in the bulkiness of their prostate tumor, reductions in prostatic acid phosphatase levels, increases in hemoglobin and red blood cell levels, and strikingly, 5 of 7 patients had complete relief of their cancer pain within 48 hours of the surgery. However, patient and physician acceptance of adrenalectomy was low, due to the morbidity of major surgery in an advanced stage cancer patient population.

1.2.1 Adrenal Androgen Inhibitor

Historical attempts to obtain the benefits of total adrenalectomy medically without the side effects of surgery have met with limited success. Aminoglutethimide and ketoconazole both inhibit several adrenal enzymes involved with adrenal androgen synthesis. Modest therapeutic activities on prostate cancer were observed. However, the side effects were significant. For example, in combination with hydrocortisone, aminoglutethimide resulted in a PSA response proportion of 37% with median response duration of 8.6 months in a Phase 2 study [19] at the expense of lethargy, skin rash, hypothyroidism, nausea and vomiting. Its use has been limited [19, 20].

Ketoconazole inhibits several adrenal enzymes required for steroid biosynthesis. Its efficacy in prostate cancer is comparable to that of aminoglutethimide. Pilot studies in patients after failure of combined androgen blockade where ketoconazole was given simultaneously with anti-androgen withdrawal (AAWD) showed that 55% of patients achieved a 50% PSA decline [21]. When administered after AAWD, 36%-62.5% of patients had a 50% PSA decline [22, 23]. In a Phase 3 study conducted by Cancer and Leukemia Group B, PSA response rate was 27% with a median duration of response of 9 months in the group of patients randomized to the combination arm of AAWD and ketoconazole plus hydrocortisone versus the AAWD alone arm [24]. However, ketoconazole inhibits CYP3A4 with substantial risk of drug-drug interactions, such as warfarin and statins [25]. It is often poorly tolerated by patients, with commonly occurring side effects including diarrhea, nausea, vomiting, and depression [21, 23, 24]. In one Phase 3 study, 20% of patients discontinued therapy prematurely due to treatment toxicity [22]. To date, ketoconazole remains a treatment to be used by physicians experienced in managing toxicities when patients have exhausted other options.

1.2.2 Glucocorticoids

Glucocorticoids such as prednisone, dexamethasone, and hydrocortisone have been frequently administered as standard of care in advanced prostate cancer because of their modest antitumor activity and palliative effects on disease. Two prospective Phase 3 studies have documented the safety and palliative benefit of prednisone. Prednisone 7.5-10 mg daily was examined among 81 patients in one arm of a Canadian Phase 3 trial, with 22% of patients achieving a 50% PSA decline and a median time to progression of 4.0 months [26]. Likewise, in a European Phase 3 study control arm where 201 patients were treated with prednisone 5 mg twice daily, PSA decline of ≥ 50% was observed in 21% of patients [27]. Significant improvements in pain, qualify of life and fatigue were also reported.

Other glucocorticoids have similar activity in advanced prostate cancer. Hydrocortisone has been evaluated as a control arm in prospective Phase 3 studies. In one study, 231 patients treated with hydrocortisone alone (control arm) showed that 16% of patients achieved a PSA decline of ≥50% with a median duration of response of 2.5 months [28]. Similarly, 14% of patients given hydrocortisone 40 mg daily achieved a PSA decline ≥ 50% lasting a median of 2.3 months in a Cancer and Leukemia Group B (CALGB) study [29]. The antitumor activity of hydrocortisone was slightly lower than prednisone in these Phase 3 studies (14%-16% PSA response rate for hydrocortisone versus 21%-22% PSA response rate for prednisone; median duration of response also favored prednisone). Likewise, dexamethasone has antitumor activity in prostate cancer [30, 31, 32]. No prostate cancer trials have directly compared 2 glucocorticoids.

1.2.3 Chemotherapy and Bisphosphonates

Several agents have been approved as palliative therapy for prostate cancer. Estramustine was approved in the 1970s. However, in a randomized study where overall survival was compared, diethystilbesterol was found to be superior to estramustine [33]. In 1996, mitoxantrone and prednisone were approved for palliation of pain and improvement in

quality of life in a randomized study with prednisone as control [26]. However, there was no survival benefit. Recently, zoledronic acid was approved for reduction in skeletal morbidity in solid tumors including prostate cancer, in combination with medical/surgical castration [34]. None of these agents improved the overall or prostate cancer-specific survival of patients with CRPC.

Docetaxel is the first, and only agent to date, that has demonstrated survival benefit in CRPC. In 2004, several countries approved docetaxel and prednisone based on results from the TAX-327 and Southwest Oncology Group (SWOG) 9916 studies. TAX-327 was an international Phase 3 study that randomized patients with metastatic AIPC to one of 3 treatment arms [17]. Patients who received docetaxel 75 mg/m^2 once every 3 weeks together with prednisone 5-mg orally (PO) twice per day (bid); had statistically significant improvement of overall survival over those who received docetaxel 30 mg/m^2 once every week with daily oral prednisone or those who received mitoxantrone 12 mg/m^2 every 3 weeks with daily oral prednisone. In the 3-weekly docetaxel regimen, median overall survival was 18.9 months (95% confidence interval 17.0 – 21.2), compared with the mitoxantrone arm 16.5 months (95% confidence interval 14.4 – 18.6 months). The hazard ratio for death was 0.76 (95% confidence interval 0.62 – 0.94, p =0.009) in the every 3-week docetaxel regimen as compared with the mitoxantrone arm [17].

The SWOG Study 9916 was a Phase 3 trial with similar results; 770 men were randomized to either a regimen of 3-weekly docetaxel with estramustine and dexamethasone, or a regimen of mitoxantrone and prednisone [16]. The median overall survival was 17.5 months in the docetaxel arm, and 15.6 months in the mitoxantrone arm, p=0.02. These results were consistent with the TAX-327 data.

Results from TAX-327 were recently updated at ASCO 2007 in Chicago, IL, USA. Overall survival results were maintained after the additional 2 years of follow-up and an additional 276 deaths [13]. The median survival in the docetaxel 3-weekly arm and mitoxantrone arms were the same as previously reported in 2004, 18.9 months (95% confidence interval 17.0-21.2) for docetaxel every 3 weeks plus prednisone, and 16.5 months (95% confidence interval 14.4-18.6) for mitoxantrone plus prednisone. In an exploratory subset analysis, it was interesting that most of the benefit was seen in patients who were free of pain at the time therapy was initiated. This suggests that great unmet need remains in advanced prostate cancer, particularly for an agent that improves overall survival in patients who experience pain.

1.3 Abiraterone Acetate (CB7630)

Abiraterone (CB7598) is [17-(3-pyridyl)androsta-5,16-dien-3β-ol] and is a steroidal irreversible inhibitor of CYP17 (17α hydroxylase/C17,20-lyase), blocking 2 important enzymatic activities in the synthesis of testosterone (Figure 1), based on the observation that nonsteroidal 3 pyridyl esters improved selectivity for inhibition of 17α-hydroxylase/C17,20 lyase. Abiraterone is a potent inhibitor with an apparent inhibition constant of 0.5 nM. Pharmacodynamic studies demonstrated that its effects on adrenal steroid synthesis were consistent with its mechanism of action. Antitumor effects were evident with PSA response

and durable objective responses using Response evaluation criteria in solid tumors (RECIST) criteria [35] in Phase 1 and Phase 2 studies conducted to date.

Abiraterone acetate (CB7630) is the 3-acetate analog of abiraterone and thus a pro-drug of abiraterone. The chemical nomenclature of abiraterone acetate is 3β acetoxy-17-(3-pyridyl)androsta-5,16-diene; its empirical formula is $C_{26}H_{33}NO_2$ and molecular weight is 391.55. Once absorbed after oral administration, abiraterone acetate is rapidly converted to the active form, abiraterone (Figure 2). Abiraterone was the predominant, if not the only metabolite of abiraterone acetate detected in blood both in preclinical studies [36] and in previously conducted clinical studies [37].

Figure 1. The Enzyme Complexes Inhibited by Abiraterone

FIG. 1. The impact of abiraterone on the adrenal steroid synthesis pathway. Abiraterone inhibits CYP450c17 17α-hydroxylase and $C_{17,20}$-lyase activity (crossed out in red) and suppresses androstenedione, DHEA and their androgenic precursors (blue arrows). Suppression of cortisol and its precursors causing a compensatory rise in ACTH and excess synthesis of aldosterone and its precursors is predicted (blue arrows).

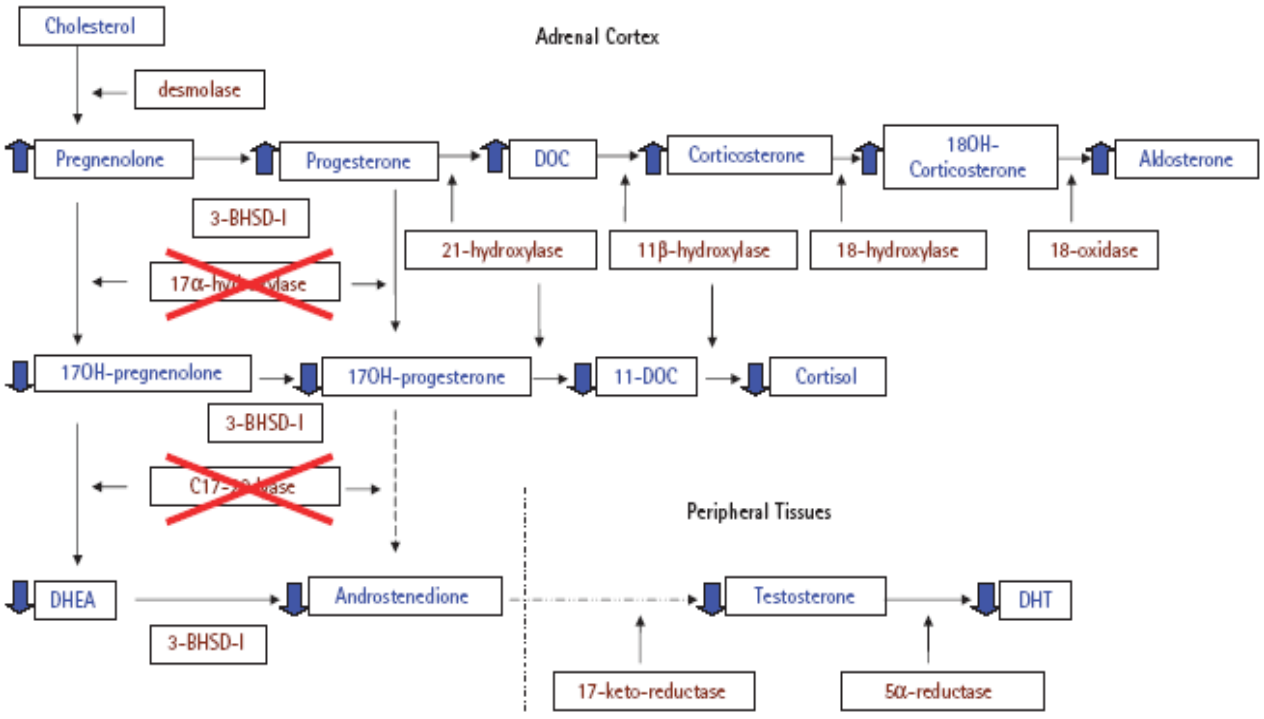
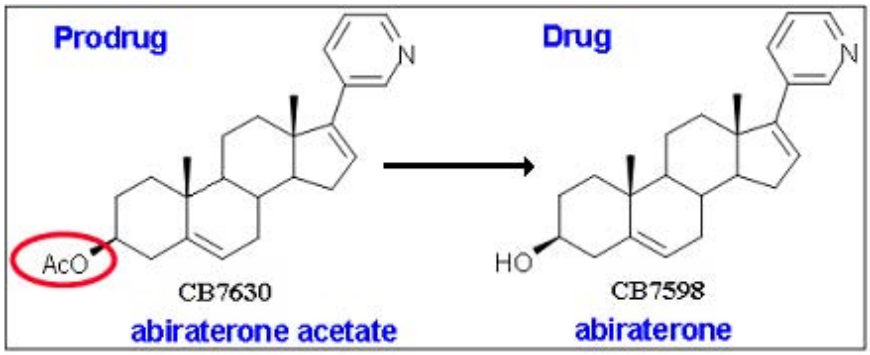


Figure 2. Prodrug Abiraterone Acetate is Converted to Abiraterone after Absorption



1.3.1 Dosing Rationale

The dose of abiraterone acetate in this study is 1000 mg daily based on results of two Phase 1 dose-finding studies. In the first Phase 1 study with capsule formulation (COUAA-001) [38], abiraterone acetate was evaluated for safety, pharmacokinetics, and its effects on adrenal steroid synthesis at dose levels ranging from 250 mg to 2000 mg. Preliminary analysis showed that abiraterone acetate was well tolerated at all dose levels. There were no hospital admissions related to study drug or any evidence of clinically significant adrenal insufficiency. Patients have been on this study for up to 18 months. In the second Phase 1 study (COU-AA-002) [39, 40] that evaluated the safety and tolerability of abiraterone acetate tablet formulation at doses ranging from 250 to 1000 mg, a daily dose of 1000 mg has also been found to be safe and well tolerated.

Consistent with abiraterone acetate's mechanism of action, hypertension (HTN), hypokalemia, and lower extremity edema were the most commonly-observed drug-related adverse events, which were all manageable with medication. Pharmacokinetic (PK) studies showed increased systemic drug exposure at higher doses. Adrenal metabolite analysis showed inhibition of CPY17 even at low doses of abiraterone acetate and a compensatory increase of corticosterone and deoxycorticosterone. Of note, antitumor activities were apparent at all dose levels tested. Data from dose-finding studies indicated that when PK, adrenal CYP17 inhibition, and efficacy signals are taken into consideration, the 1000-mg dose offered consistent pharmacological effects without additional side effects. Therefore, the 1000-mg dose has been chosen for further efficacy and safety evaluation in this Phase 3 study.

1.3.2 Concurrent Prednisone

In ongoing studies, some patients receiving abiraterone acetate have been treated concurrently with glucocorticoids, including prednisone.

Based on our understanding of the mechanism of abiraterone action and observations in patients with congenital deficiency of CYP17, we anticipated that a state of mineralocorticoid excess could occur after pharmacologic inhibition of CYP17. Resulting reduced cortisol levels may lead to a compensatory ACTH surge thereby resulting in hypertension, hypokalemia, and fluid retention [41].

As expected, when abiraterone acetate was used as a single agent in Phase 1 and 2 studies, hypertension, hypokalemia, and fluid retention were observed and were primarily CTC grade 1-2 in severity. These side effects were readily managed with potassium supplementation, eplerenone (selective mineralocorticoid antagonist), antihypertensive agents, and low dose corticosteroids. Grade 1-2 fatigue was observed in some patients and was associated with discontinuation of corticosteroids as required per Phase 2 protocol entry criteria and extended duration of treatment with abiraterone acetate. Although there was no evidence of a dose-response relationship, administration of low dose cortiscosteroids as specified in the study improved symptoms of fatigue and tolerability of abiraterone acetate, including symptoms of mineralocorticosteroid excess. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH surge and upstream adrenal steroids, suggesting that this combination may be a better tolerated and safer regimen in this older and frail patient population. Prednisone was selected over other corticosteroids because it is commonly used as standard of care in combination with approved chemotherapy agents or as a monotherapy for palliation of symptoms. The safety and efficacy evaluation of abiraterone acetate with concurrently administered prednisone is continuing in ongoing Phase 2 studies. The regimen of abiraterone acetate 1000 mg daily and low dose prednisone 5-mg bid has been chosen as the experimental intervention arm in this study.

1.3.3 Status of Current Clinical Trials of Abiraterone Acetate

Over two hundred forty (240) patients have been treated to date with abiraterone acetate, with approximately 215 patients at the 1000-mg dose level.

On August 20, 2010, the Independent Data Monitoring Committee (IDMC) met to review the interim safety and efficacy of the COU-AA-301 study. Men who were assigned to the abiraterone acetate and prednisone group had a significant improvement in survival that met the protocol-specified criteria for stopping the blinded treatment part of the study. The IDMC recommended cross-over to abiraterone acetate treatment of any patient currently being treated with placebo. There were no additional safety signals observed that would warrant a change in study management (See Section 6.7.11).

1.3.3.1 Chemotherapy-Naïve Castration-Resistant Prostate Cancer (CRPC)

Following safe expansion at the 1000-mg dose, the COU-AA-001 study enrolled additional patients to the Phase-2 portion of the study to further evaluate antitumor activity in chemotherapy-naïve CRPC patients. To date, 52 patients have been treated and 44 have reached 3 months of therapy and are evaluable for response: 27/44 (61%) have had durable PSA declines of $\geq$ 50% and 11/44 patients have had $\geq$ 90% declines in PSA. Twenty-one (21) out of 44 patients are evaluable by RECIST criteria: 12/21 have had confirmed

radiological partial responses and 7/21 ongoing stable disease lasting more than 3 months. Nine patients have received abiraterone acetate for more than 12 months [42]. Similar responses rates have been seen in COU-AA-002, a parallel Phase I study investigating tablet formulation as opposed to capsules [43].

1.3.3.2 Castration-Resistant Prostate Cancer (CRPC) Post-Docetaxel

Two Phase 2 studies (COU-AA-003 and COU-AA-04) in post-docetaxel CRPC patients are also being conducted. Preliminary results are available from the COU-AA-003 study. Twenty-eight evaluable patients have been recruited to date. Fourteen of the 28 patients have achieved PSA declines $\geq$ 50% and the median time to PSA progression is 167 days (24 weeks). Eighteen patients had measurable lesions at baseline and 4 (22%) of these had a confirmed radiologic PR. One patient has been on treatment for more than a year. To date, no relationship has been found between true progression on prior docetaxel chemotherapy or stopping docetaxel for another reason such as toxicity, and response to abiraterone. The drug has been well tolerated in the post-docetaxel setting with similar toxicities to pre-docetaxel patients. (Refer to the current version of the abiraterone acetate Investigator's Brochure for additional or updated information.)

1.4 Clinical Benefits of Current Treatment

1.4.1 Quality of Life Assessments

Observational studies have documented a rapid decline in health status in CRPC. A population-based sample of 1,243 patients was followed in Sweden during the year prior to their death from prostate cancer using the brief pain inventory short form (BPI-SF) and the Euro EQ-5D quality of life survey instruments. Declines across scales were highest in the 8 months preceding death [44]. Similarly, Litwin et al [45] and Melmed et al [46] assessed qualify of life (QOL) in metastatic prostate cancer patients in CaPSURE database from the United States. Declines across all 8 domains measured by the SF-36 were found during the 12 months prior to death.

In contrast to observational studies, the TAX-327 interventional study found that global QOL measured by the FACT-P was improved for both docetaxel regimens [17], although only the 3-weekly docetaxel arm but not the weekly docetaxel arm had improved survival over mitoxantrone in this study. SWOG 99-16 study, a significant survival advantage was found for docetaxel plus estramustine compared with mitoxantrone and prednisone; QOL was assessed with the EORTC-QLQ-C30 instrument and the prostate subscale PR25 QOL [47] and pain palliation did not favor either study arm. In the Canadian study comparing mitoxantrone and prednisone with prednisone alone in advanced prostate cancer, the PROSQOLI and EORTC QLQ-C30 and prostate specific subscale QOLM-P14 were used, demonstrating that patients in the mitoxantrone arm had greater and longer lasting improvements in QOL [48].

Though there is no consensus on the best QOL instrument to use in interventional trials, the FACT-P has been selected for use in this trial based on several factors: 1) its content and psychometric properties have been well validated [49], and 2), clinically meaningful changes

in the FACT-P have been determined by validation comparisons with clinical measures of disease burden [50].

1.4.2 Pain Assessment and Stratification

1.4.2.1 Background

Pain experienced by patients with advanced prostate cancer is multifactorial. Not only nociceptive pain (that can be adequately treated using opioids), but also prominent neuropathic pain is present due to metastases compressing nerve roots. Pain medications including opioids, NSAIDs, tricyclics and other agents active in the central nervous system have been the mainstay for pain palliation in advanced prostate cancer.

Pain is significantly associated with overall survival in advanced prostate cancer. For example, in TAX 327 [51, 52, 53, 13] the McGill Pain Questionnaire (MPQ) (PPI score 0-2 versus 3-5) successfully stratified the survival of first line chemotherapy patients.

The BPI-SF, a numeric rating scale (NRS), was selected as the pain instrument for the COU-AA-301 study due to the high correlation of numeric rating scales with verbal descriptor scales (e.g. MPQ PPI) [54], its validation in multiple languages appropriate for participating study centers, and its prior use in metastatic prostate cancer studies [55, 28, 56]. The BPI-SF assesses both the intensity of pain and the interference in patient's function caused by their pain [57].

1.4.2.2 Pain Stratification

The pain stratification definition for this study was selected because the majority of patients with BPI scores of 4 consider themselves to have moderate rather than mild pain [58]. Pain $\geq$ 4 on the BPI-SF item worst pain over the last week correlated with poor survival in advanced prostate cancer [44], with approximately 50% of men who died of prostate cancer reporting pain score $\geq$ 4 as compared to approximately 25% of men in the overall study population.

1.4.2.3 Pain Palliation

The pain palliation definition for this study, 30% decrease in BPI-SF score in the absence of an increase in analgesic usage, was selected because patients consider this to be a meaningful decrease in pain [59]. A 30% or two (2)-point decline in intensity has been established as the smallest clinically meaningful change in the BPI-SF in efficacy studies of new analgesics [59]. The BPI-SF data in this study will also be analyzed using the continuous proportion of responders graph that can help to illustrate the overall benefits of an intervention on pain without necessitating selection of a cutoff to define pain response [60].

1.4.2.4 Pain Progression

Pain progression in COU-AA-301 is defined as an increase of $\geq$ 30% in the worst pain over the past 24 hours on the BPI-SF observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score $\geq$ 30% observed at

2 consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4.

1.4.2.5 Analgesic Score

In this study, analgesic usage will be scored according to the WHO analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including NSAIDs, paracetamol/acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain [44].

1.5 Circulating Tumor Cells in Castration-Resistant Prostate Cancer (CRPC)

The enumeration of circulating tumor cell (CTC) number using the Cell Search Technology is an analytically valid biomarker that has been clinically qualified to monitor the effectiveness of therapy in patients with metastatic breast cancer [61, 62, 63, 64]. Studies that analyzed CTCs in patients with castration resistant prostate cancer have shown that the cells isolated are positive by immunohistochemistry for PSA and α-methyl CoA racemase (a specific marker for prostate cancer) and that they retain known genomic alterations associated with prostate cancer including AR gene amplification, TMPRSS-Erg gene fusions and Myc amplification.[65, 66, 67].

Preliminary studies suggest that CTC counts may also predict survival and response to therapy in CRPC. In a small pilot study, univariate analyses demonstrated that a CTC count of ≤ 5 or > 5 correlated with overall survival (0.002; HR=7.37); in multivariate analyses CTC counts and PSA doubling time were the only 2 independent predictors of outcome unlike PSA, Gleason score, presence or absence of bone metastases, and age [68].

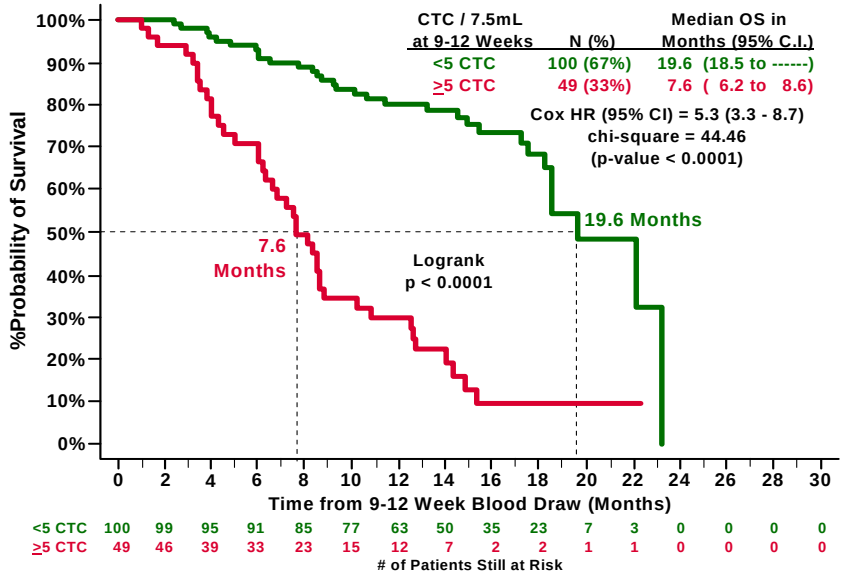
The CTCs have been detected in 19/49 (39%) and 21/28 (75%) of chemotherapy-naïve patients and post-docetaxel patients, respectively, who have participated in the Phase 1-2 trials of abiraterone acetate at The Institute of Cancer Research and The Royal Marsden Hospital in the United Kingdom [42]. Similarly, CTC counts > 5/7.5 mL have been detected in 32/47 (70%) of post-docetaxel CRPC patients enrolled in abiraterone acetate trials at Memorial Sloan Kettering Cancer Institute, consistent with the results from the United Kingdom (Scher H, unpublished observation, 2007). A general trend has been seen for falling CTC counts in responders by PSAWG criteria and RECIST, and a trend for rising CTC counts in non-responders by Prostate Specific Antigen Working Group (PSAWG) and RECIST criteria.

IMMC-38 is the third in a series of trials (IMMC 01, 06, 38) designed to relate circulating tumor cell number, analyzed with the CellSearch technology to clinical outcomes in patients with metastatic breast, metastatic colorectal or metastatic prostate cancer. [69] In IMMC-38, CTC counts were measured at discrete time intervals after the initiation of cytotoxic therapy, and studied as predictors of overall survival, and as means of monitoring patients undergoing treatment for these diseases. The primary endpoint was the ability of CTC counts after the initiation of cytotoxic therapy to predict overall survival (power 80%). At the time of this analyses, a total of 119 (52%) of the 231 evaluable patients have died, and the median overall

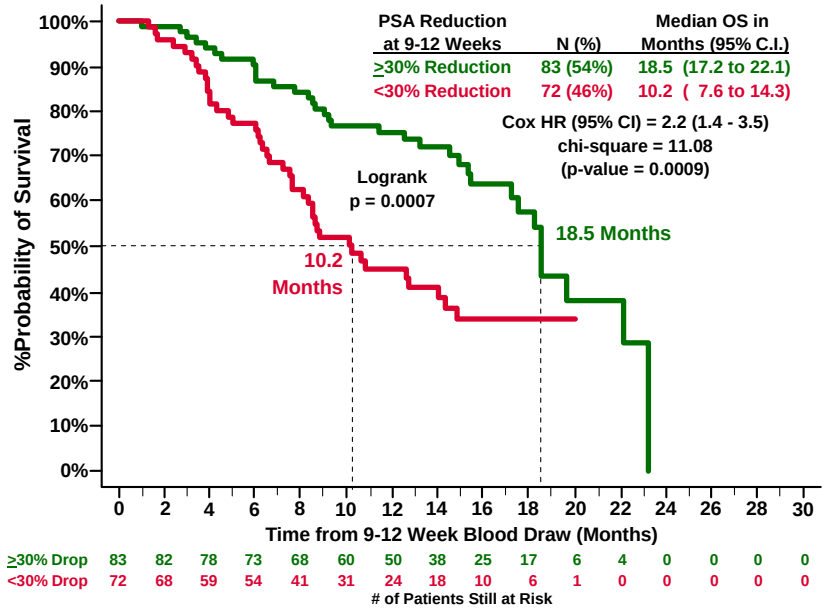
survival for the 231 evaluable patients was 17.2 months (95% CI = 14.2 to 21.0 months). The results, illustrated graphically, show how the normalization (CTC number < 5) 9 to 12 weeks after initiation of cytotoxic therapy was a better predictor of overall survival than a reduction in PSA.

Overall survival 9-12 weeks after the Initiation of Therapy for patients with Favorable and Unfavorable CTC (Panel A) and Favorable and Unfavorable PSA Changes (Panel B)

A. CTC



B: PSA Reduction



In this study, we will further explore the potential relationship between changes in CTCs and its possible utility as a surrogate for clinical benefit. Specifically, we seek to determine whether a 5 week (cycle 2), 9 week (cycle 3) or 13 week (Cycle 4) CTC number below 5/7.5mL correlates with treatment outcome (ie, survival), recognizing that the demonstration of surrogacy requires multiple studies. Fluorescence in situ hybridization (FISH) for AR gene amplification and TMPRSS2-ETS gene translocations will also be investigated as an optional assessment in selected sites.

1.6 Rationale for Study Design and Control Group

The mechanisms of action of abiraterone acetate and docetaxel are not overlapping. Abiraterone acetate has shown promising antitumor activity by reducing adrenal androgen production, whereas docetaxel-based chemotherapy targets microtubule dynamics. In a recently conducted Phase 2 study where abiraterone acetate was administered to patients with advanced prostate cancer who had progressive disease after docetaxel-based chemotherapy, approximately half of the patients had a PSA reduction of $\geq$ 50%. In patients with soft tissue metastasis on imaging studies, tumor shrinkage was observed as well. Therefore, it appears that resistance to docetaxel is independent of sensitivity to androgen-deprivation therapy.

The glucocorticoids, such as prednisone or dexamethasone, are an integral component of docetaxel-based chemotherapy, and are frequently used in combination with other marketed chemotherapeutic agents, such as mitoxantrone, in CRPC. It is a common clinical practice to continue glucocorticoids even after patients have been discontinued from chemotherapy. A Phase 2 study was conducted to evaluate the safety and efficacy of abiraterone acetate in CRPC after failing docetaxel-based chemotherapy while receiving low dose prednisone. Preliminary data so far shows few adverse events. In particular, adverse events known to be associated with abiraterone acetate monotherapy, namely, hypokalemia, hypertension, and fluid retention appear to be less frequent when abiraterone acetate is used in combination with low-dose prednisone. In this Phase 3 prostate cancer study, prednisone 5 mg bid has been selected for use in both study treatment groups. The use of prednisone as a single agent, sometimes prescribed to palliate symptoms in advanced CRPC also justifies the placebo-controlled design where the placebo group will receive low dose prednisone rather than no treatment.

The primary hypothesis of this randomized, double-blind, placebo-controlled study is that patients receiving abiraterone acetate and prednisone will achieve a 25% improvement in overall survival compared with patients receiving placebo and prednisone. It is also anticipated that abiraterone acetate will increase the proportion of patients gaining PSA responses as defined by PSAWG criteria, prolong the PSA and radiographic progression-free survival, possibly palliate pain, reduce skeletal-related events due to metastatic bone disease, and improve QOL.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is to compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of which contains docetaxel.

2.2 Secondary Objective(s)

The secondary objectives of this study are:

- To further evaluate the safety profile of abiraterone acetate plus prednisone.
- To further characterize the PK of abiraterone acetate when administered concurrently with prednisone.
- To further explore the potential utility of CTCs as a surrogate for clinical benefit
- To evaluate the impact of abiraterone acetate plus prednisone on health related quality of life (QOL).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled study with a randomization allocation ratio of 2:1 (abiraterone acetate: placebo). This study will be conducted at approximately 175 investigative sites and approximately 1158 patients will be enrolled.

3.1.1 Primary Efficacy Endpoint

The primary study endpoint is overall survival, defined as the time from randomization to death from any cause.

3.1.2 Secondary Efficacy Endpoints

- Proportion of patients achieving a PSA decline ≥ 50% according to protocol-specific PSAWG criteria
- Time-to-PSA progression based on protocol-specific PSAWG criteria
- Progression-free survival (PFS) based on imaging studies

3.1.3 Other Study Endpoints

- Proportion of patients with objective tumor response by modified RECIST (baseline LN size must be ≥ 2 cm to be considered a target lesion)

- Proportion of patients experiencing pain palliation using BPI-SF and analgesic score
- Time to pain progression
- Time to first skeletal-related event
- Modified PFS based on criteria for discontinuation of study treatment
- Proportion of patients achieving a decline in CTCs/7.5ml to less than 5
- QOL total score and each subscale score as assessed by FACT-P

3.1.4 Safety Assessments

- Medical history, vital sign measurements, physical examination, and body weight
- Concomitant therapy and procedures
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Appendix 5)
- Blood chemistry, hematology, coagulation studies, serum lipids, and urinalysis
- Electrocardiograms (ECGs) and measurement of cardiac ejection fraction

3.1.5 Other Assessments

- Quality of Life (QOL) using FACT-P Quality of Life questionnaire
- Fatigue evaluated in the Brief Fatigue Inventory (BFI) instrument
- Medical resource utilization (MRU) information
- PK measurements
- CTC enumerations

3.1.6 Study Duration and Dates

The study period will consist of screening, treatment, and follow-up periods. In this study, patients will receive study treatment (abiraterone acetate or placebo) plus prednisone until progression of clinical disease. Follow-up will continue until patient dies, is lost to follow-up, or withdraws informed consent up to 60 months (5 years).

3.1.7 Study Activities

3.1.7.1 Screening Period

All patients must sign a written informed consent form before study specific screening procedures are performed. Informed consents may be obtained up to 30 days prior to Cycle 1 Day 1. Screening procedures to evaluate patient eligibility for the study will be conducted within 14 days prior to Cycle 1 Day 1. If the patient meets eligibility and screening requirements he will be randomized and will return to the site for the Cycle 1 Day 1 visit and dosing.

3.1.7.2 Randomization

Once eligibility is confirmed, patients will be randomized to a treatment group according to the randomization schedule. All patients must commence treatment within 72 hours (3 calendar days) of randomization.

3.1.7.3 Treatment Period

Randomized patients will have Cycle 1 Day 1 procedures and receive study treatment (abiraterone acetate or placebo) that will subsequently be administered orally once daily. Patients who participate in the pharmacokinetics testing will take their Day 1 dose on Cycles 1, 2 and 5 in the clinic. All patients will also take 5 mg of prednisone or prednisolone orally twice daily. In regions where prednisone is not marketed or available, prednisolone will be provided. If a patient has been receiving glucocorticoids other than prednisone or prednisolone, it will be necessary to switch the glucocorticoid to prednisone or prednisolone 5 mg bid prior to Cycle 1 Day 1.

No crossover will be permitted between the 2 treatment groups. Each cycle of treatment will be 28 days. Patients will return for Cycle 1 Day15 visit ± 3 days visit to evaluate safety and dosing compliance (a count of study drug tablets). From Cycle 2 to End-of-Study, Day 1 visits will occur every 28 days with a ± 2 day window. Study windows are to be calculated from Cycle 1 Day 1 date, and if utilized, every effort will be made for the patient to return to schedule. Patients may have additional imaging visits up to 8 days before Cycles requiring images (Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 10 Day 1 and every 3rd Cycle and beyond Cycle 10) or at Treatment Discontinuation Visit.

3.1.7.4 Treatment Period Following Study Unblinding

Pursuant to the IDMC's recommendation on August 20, 2010, all patients will be unblinded and patients who have received placebo will be offered cross over therapy with abiraterone acetate. The study schedule for all patients is as follows:

- Patients who are currently receiving placebo or are in long term follow up after receiving placebo will follow the schedule entitled, "Starting Abiraterone Acetate AFTER Placebo"

- Patients who are currently receiving abiraterone acetate will follow the schedule entitled, "Continuing Abiraterone Acetate Treatment"

Treatment will be continued until patients have clinical progression as determined by the Investigator, or until they meet the following criteria for withdrawal in Section 6.9:

- Dosing compliance

- Sustained side effects

- Initiation of new anti-cancer treatments

- Administration of prohibited medications
- Patient withdraws consent

Patients who are crossing over must meet all of the criteria for cross over therapy listed below.

Criteria For Cross Over Therapy with Abiraterone Acetate

1. Willing to provide written informed consent
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2. (Appendix 6)
3. Hemoglobin ≥ 8.0 g/dL independent of transfusion
4. Platelet count ≥ 50,000/µL
5. Serum albumin ≥ 2.5 g/dL
6. Serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min
7. Serum potassium ≥ 3.5 mmol/L
8. Able to swallow the study drug whole as a tablet
9. No serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection.
10. Liver functions as follows:
    - Serum bilirubin < 1.5 x ULN (except for patients with documented Gilbert's disease, where the upper limit of serum bilirubin is 3 mg/dL)
    - AST or ALT < 2.5 x ULN (for patients with known liver metastasis, AST or ALT < 5 x ULN is allowed)
11. Blood pressure as follows: systolic BP ≤ 160 mmHg and diastolic BP ≤ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is within these limits while receiving anti-hypertensive therapy.
12. No active or symptomatic viral hepatitis or chronic liver disease
13. No clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of < 45 % at baseline
14. Recovered from the acute toxicities due to prior chemotherapy or radiotherapy (resolved to a NCI CTCAE (version 3.0) grade of ≤ 1). Chemotherapy induced alopecia and grade 2 peripheral neuropathy are allowed (Appendix 5)
15. At least 30 days since last treatment with an investigational drug or device (with the exception of abiraterone acetate/placebo in study COU-AA-301)
16. No condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study
17. Willing to comply with the procedural requirements of this protocol
18. Willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after last study drug administration.

The following schedule of events should be followed by patients receiving placebo at the time of unblinding or in long term follow up after receiving placebo:

SCHEDULE OF EVENTS

STARTING ABIRATERONE ACETATE AFTER PLACEBO

Table of Scheduled Events

Evaluation	Screening Day -30 to 1	Treatment Phase				Long-Term Follow-Up Phase (contact every 3 months)
		New Cycle 1 Day 1 and Day 1 of every cycle thereafter	New Cycles 1, 2, and 3, Day 15	New Cycle 1 Day 1 and Day 1 of every 3rd cycle thereafter	Post-Unblinding End-of-Study Visit[a]	
Signed consent form[b]	X					
New medical history and prior prostate therapies[c]	X					
Physical examination (including body weight)	X	X			X	
Vital signs[d]	X	X			X	
ECOG performance status	X	X			X	
12 Lead ECG[e]	X			X	X	
MUGA scan or cardiac ECHO[f]	X				X	
Adverse event assessment[g]	X	X	X		X	
BPI-SF, analgesic usage	X	X			X	
Concomitant medication	X	X			X	
Overall survival[j]						X
Laboratory Assessments[k]						
CBC	X	X			X	
Coagulation Factors - PT/PTT (INR)	X	X			X	
Serum chemistry, electrolytes[h]	X	X	X		X	
Serum Lipids	X					
PSA[i]	X			X	X	

ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MUGA=Multiple Gated Acquisition Scan; PSA= prostate specific antigen

[a] End-of-Study visit should be scheduled to collect safety assessments approximately 30 days after the subject discontinues treatment.

[b] Written informed consent must be obtained within 30 days prior to New Cycle 1 Day 1.

[c] Applicable only to placebo-treated subjects who entered long-term follow-up after COU-AA-301 participation.

[d] Vitals Include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

[e] An ECG should be obtained prior to Day 1 visit, every 3 cycles, and at End of Study visit. ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.

[f] A MUGA scan should be obtained at the new baseline, and the window for the MUGA may be up to 90 days prior to the new Cycles. Echocardiography can be used if MUGA is not available or when echocardiography is standard of care at the study site.

[g] Pre-treatment serious adverse events should be reported from time subject signs a consent form up to Day 1 of treatment administration. (Applicable only to placebo-treated subjects who entered long-term follow-up after COU-AA-301 participation.)

[h] At C1D15, C2D15 and C3D15 Chemistry is limited to Liver Function Tests: AST, ALT, alkaline phosphatase, and total bilirubin.

[i] If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE.

[j] Overall survival may be collected by telephone interview or chart review.

[k] Screening labs for patients who were taking placebo at the time of unblinding may use central laboratory values from their last cycle. If PSA was not collected during the last cycle then PSAwill be required.

The following schedule of events should be followed by patients currently on active abiraterone acetate:

SCHEDULE OF EVENTS

CONTINUING ABIRATERONE ACETATE TREATMENT

Table of Scheduled Events

Evaluation	Treatment Phase			
	New Cycle 1 Day 1 and Day 1 of every cycle thereafter	**New Cycle 1 Day 1 and Day 1 of every 3rd cycle thereafter**	**Post-Unblinding End-of-Study Visit[b]**	**Long-Term Follow-Up Phase (contact every 3 months)**
Signed consent form[a]	X			
Physical examination (including body weight)	X		X	
Vital signs[c]	X		X	
ECOG performance status	X		X	
12 Lead ECG[d]		X	X	
Adverse event assessment[e]	X		X	
MUGA scan or cardiac ECHO			X	
BPI-SF, analgesic usage	X		X	
Concomitant medication	X		X	
CBC	X		X	
Coagulation Factors - PT/PTT (INR)	X		X	
Serum Chemistry, electrolytes	X		X	
PSA[f]		X	X	
CTC Assessment			X	
Overall survival[g]				X

ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; MUGA=Multiple Gated Acquisition Scan; PSA = prostate specific antigen

[a] Written informed consent must be obtained within 30 days prior to New Cycle 1 Day 1.

[b] End-of-Study visit should be scheduled to collect safety assessments approximately 30 days after the subject discontinues treatment.

[c] Vitals Include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

[d] An ECG should be obtained prior to Day 1 visit, every 3 cycles, and at End of Study visit. ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.

[e] Pre-treatment serious adverse events should be reported under processes established for Study COU-AA-301.

[f] If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE.

[g] Overall survival may be collected by telephone interview or chart review.

3.1.7.5 Follow-up Period

During the Follow-up period, overall survival follow-up should be performed every 3 months for up to 60 months (5 years) and may be collected by telephone interview or chart review.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 1158 medically or surgically castrated male patients with metastatic CRPC who have failed docetaxel-based chemotherapy will be enrolled from approximately 175 global study sites.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Willing and able to provide written informed consent
2. Written Authorization for Use and Release of Health and Research Study Information (US sites only) or Data Protection Consent (European sites only) has been obtained.
3. Age ≥ 18 years and male
4. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
5. At least one but not more than 2 cytotoxic chemotherapy regimens for metastatic castration-resistant prostate cancer. At least one regimen must have contained docetaxel. If docetaxel-containing chemotherapy is used more than once, this will be considered as one regimen.
6. Documented prostate cancer progression as assessed by the investigator with one of the following:
   a. PSA progression according to PSAWG criteria.

      - Patients on systemic glucocorticoids for the treatment of prostate cancer or control of symptoms must have documented PSA progression by PSAWG criteria prior to Cycle 1 Day 1. Patients with confirmed PSA progression while on systemic glucocorticoids other than prednisone or prednisolone are required to switch to prednisone or prednisolone 5 mg twice daily prior to Cycle 1 Day 1, but PSA progression does not have to be reconfirmed.

   b. Radiographic progression in soft tissue or bone with or without PSA progression.

7. Ongoing androgen deprivation with serum testosterone < 50 ng/dL (< 2.0nM)
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2. (Appendix 6)
9. Hemoglobin ≥ 9.0 g/dL independent of transfusion
10. Platelet count ≥100,000/µL
11. Serum albumin ≥ 3.0 g/dL
12. Serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min
13. Serum potassium ≥ 3.5 mmol/L
14. Able to swallow the study drug whole as a tablet

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection.
2. Abnormal liver functions consisting of any of the following:
   - Serum bilirubin ≥ 1.5 x ULN (except for patients with documented Gilbert's disease)
   - AST or ALT ≥ 2.5 x ULN, (for patients with known liver metastasis, AST or ALT ≤ 5 x ULN is allowed)
3. Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy.
4. Active or symptomatic viral hepatitis or chronic liver disease
5. History of pituitary or adrenal dysfunction
6. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline
7. Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 12 months
8. Known brain metastasis
9. History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug
10. Prior therapy with abiraterone acetate or other CYP17 inhibitor(s), or investigational agent(s) targeting the androgen receptor for metastatic prostate cancer.
11. Prior therapy with ketoconazole for prostate cancer
12. Surgery or local prostatic intervention within 30 days of the first dose. In addition, any clinically relevant sequelae from the surgery must have resolved prior to Cycle 1 Day 1
13. Radiotherapy, chemotherapy or immunotherapy within 30 days, or single fraction of palliative radiotherapy within 14 days of administration of Cycle 1 Day 1
14. Any acute toxicities due to prior chemotherapy and/or radiotherapy that have not resolved to a NCI CTCAE (version 3.0) grade of ≤ 1. Chemotherapy induced alopecia and grade 2 peripheral neuropathy is allowed (Appendix 5).
15. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1
16. Condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study
17. Not willing to comply with the procedural requirements of this protocol
18. Patients who have partners of childbearing potential who are not willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after last study drug administration.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

After unblinding at Interim Analysis, all patients will receive open label abiraterone acetate. Therefore, sections 5.4 and 5.5 are no longer applicable.

5.1.1 Study Drug

Abiraterone acetate 250-mg tablets are oval, white to off-white and contain abiraterone acetate and compendial (USP/NF/EP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration (the water is removed during tabletting).

5.1.2 Placebo

Placebo will be provided as a tablet formulation and will be matched in size, color (white to off-white), and shape (oval) to abiraterone acetate tablets in order to maintain the study blind.

5.1.3 Prednisone

Prednisone (5-mg tablets) will be prescribed or provided. In regions where prednisone is not marketed, prednisolone will be substituted.

Prednisone tablets are open label.

5.2 Treatments Administered

5.2.1 Abiraterone Acetate/Placebo (Study Treatment)

Patients will be instructed to take 4 tablets (abiraterone acetate or placebo) orally (PO) at least 1 hour before a meal or 2 hours after a meal any time up to 10 pm every day.

5.2.2 Prednisone

Patients will be instructed to take 5mg prednisone, twice daily.

5.3 Selection and Timing of Dose for Each Patient

Each treatment cycle consists of 28 consecutive days. Patients may take study treatment (abiraterone acetate or placebo) until disease progression. At the time of disease progression, study treatment will remain blinded. Study treatment will be discontinued and dose of prednisone will be gradually reduced if clinically indicated.

It is not required for the prednisone to be taken with study treatment (abiraterone acetate or placebo) at the same time. The dose of prednisone will remain unchanged in the event that

the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up.

5.4 Randomization Procedures

Patients will be randomized after the investigator has verified that all eligibility criteria have been met. Patients will be randomized to receive abiraterone acetate plus prednisone or placebo plus prednisone in a 2:1 ratio. Patients will be stratified according to baseline ECOG performance status (0-1 versus 2), presence or absence of pain (pain will be classified as present when screening BPI-SF score for worst pain is at least 4; patients who do not meet this criteria are considered to have no pain for stratification purposes), 1 versus 2 prior chemotherapy regimens, and documented type of prostate cancer progression at entry (PSA progression only versus radiographic progression in bone or soft tissue with or without PSA progression).

Patients withdrawn from the study will not be replaced.

Randomization will take place across all study sites using a centralized Interactive Web Response System (IWRS). At randomization, the IWRS will assign a unique patient identification number to each patient. The patient's identification number will be used on all study-related documents including case report forms (CRFs). A treatment number will also be assigned to each patient. This treatment number is the link between a patient's CRF and blinded treatment group assignment. Patient identification numbers will not be reused.

All patients must commence treatment within 72 hours (3 calendar days) of randomization. No patient may be randomized to receive a treatment number prior to confirmation of diagnosis of prostate carcinoma.

If the study is terminated after an interim analysis, patients who are on study should continue with their protocol-defined scheduled visits.

5.5 Blinding

This is a randomized, double-blind study. Patients will receive abiraterone acetate plus prednisone or placebo plus prednisone. The following precautions are to be taken to ensure that blinding is adequately maintained throughout the study.

5.5.1 Randomization Codes

The treatment to which a patient is assigned will be determined by IWRS Section 5.4. A randomization schedule will be generated and maintained within the IWRS. All study personnel will be blinded to the patient treatment assignments.

5.5.2 Laboratory Tests Results

In order to maintain the blind, the Central Laboratory will not send results of post-treatment testosterone, other androgen measurements, CTCs, or PK to the sites and will not transfer results to the clinical database until database lock.

5.5.3 Accidental Unblinding

If a patient's treatment assignment is accidentally unblinded, that patient should remain in the study and continue treatment with the assigned treatment and all protocol tests and assessments. Unblinding information will be captured in the CRF.

5.6 Concomitant Therapy

The use of any concurrent drug from screening and while on study, prescription or over-the-counter, is to be recorded on the patient's CRF along with the reason the drug was taken.

Concurrent enrollment in another clinical investigational drug or device study is prohibited.

Supportive care medications are permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded.

The following supportive care medications are considered permissible during the study:

- Luteinizing hormone-releasing hormone (LHRH) agonists to maintain testosterone <50ng/dL
- Conventional multivitamins, selenium and soy supplements
- Additional systemic glucocorticoid administration such as "stress dose" glucocorticoid is permitted if clinically indicated for a life threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug
- Bisphosphonate usage is allowed only if patients are on the medication prior to Study Day 1
- Transfusions and hematopoietic growth factors per institutional practice guidelines
- If the permissibility of a specific drug/treatment is in question, please contact the study sponsor

The following interventions are permissible if the patient has a documented progression event but has not met all three criteria (Section 6.8) for discontinuation of treatment:

- Palliative Radiation – one course of involved field radiation (single or multi-fraction) to a single site; radiation to more than one site of disease will **NOT** be permitted
- Bisphosphonates – addition of a bisphosphonate or changing the type of bisphosphonate will only be allowed if a new SRE or bone progression is documented
- Glucocorticoids – an increase in the dose of prednisone or prednisolone or addition of a more potent glucocorticoid such as dexamethasone to treat prostate cancer related

signs and symptoms, such as fatigue and pain, will be considered a disease progression event.

5.7 Restrictions

The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment Phase. Use of other investigational drug therapy for any reason is prohibited.

Concomitant therapy with any of the following listed is restricted:

- 5 α-reductase inhibitor
- Chemotherapy
- Immunotherapy
- Ketoconazole, diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm)
- Aldactone, Spironol (spironolactone)

The decision to administer a prohibited drug/treatment should be made based on the consideration of the safety of study participant.

Patients who require the use of any of these agents will be discontinued from study-treatment phase and entered into the follow-up phase and followed for safety outcomes and overall survival assessments.

5.8 Potential for Drug-Drug Interactions

Strong inhibition of P450 CYPs 2C19, 2D6 and 1A2 by abiraterone acetate was observed in *in vitro* preclinical studies. However, these inhibitory effects of abiraterone acetate were an order of magnitude weaker than those for classic inhibitors of 1A2 and 2D6, and 5 fold weaker than for classic inhibitors of 2C19. No clinically significant drug-drug interactions have been reported to Cougar Biotechnology as of the date of this protocol. However, investigators should keep in mind the possibility that abiraterone acetate may interact with concomitant medications, particularly those that are metabolized or activated by P450 CYPs 2C19, 2D6 and 1A2. If at any time an investigator suspects a drug-drug interaction due to abiraterone acetate therapy, an adverse event report should be filed with Cougar Biotechnology. Additional information is provided in the abiraterone acetate Investigator's Brochure.

5.9 Treatment Compliance

A current and accurate account of the number of investigational tablets the investigator received from Cougar, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Cougar or its representative or

destroyed on site during and at the completion of the study must be maintained. A detailed inventory must be completed for the study treatment.

5.10 Packaging and Labeling

Abiraterone acetate or placebo tablets will be provided to each site packaged for patient assignment at the time of randomization. Patients will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 2 day window.

Information presented on the labels for investigative product will comply with applicable local regulations.

Site pharmacist will dispense the blinded study treatment to each patient in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure.

5.11 Storage

5.11.1 Pharmacy Storage Requirements

The study treatment must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol.

Bottles of study treatment should be stored at a room temperature between 15º-30º C with the cap on tightly and should not be refrigerated. Additional information is provided in the abiraterone acetate Investigator's Brochure.

5.11.2 Storage Requirements For The Patient

Bottles of study treatment should be stored at room temperature with the cap on tightly and should not be refrigerated. Patients should be advised to keep all medications out of the reach and out of sight of children.

5.12 Investigational Product Retention and Accountability at Study Site

At the time of delivery of study treatment to the site, the investigator, designee, or Pharmacist (where appropriate) will sign a drug receipt form to confirm that the supplies for the study have been received. This form will specify supply, lot numbers, quantities shipped/delivered, and date of receipt. The form will also contain statements confirming that the study treatment has been received in good condition.

Study treatment must be stored in a secure location at room temperature between 15ºC-30º C. Accountability for study treatment is the responsibility of the investigator. More details concerning this responsibility are included in Appendix 2.

Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to patients enrolled in this study. Once the study treatment is prepared for a patient, it can only be administered to that patient.

The study site must maintain accurate records demonstrating dates and amount of study treatment (abiraterone acetate, placebo, and if applicable, prednisone) received, to whom dispensed (patient by patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Cougar or its representative.

Study site staff should refer to Appendix 2, information located in the Pharmacy manual, and the Investigator's Brochure for specific instructions on the handling, storage, and administration of the study drug.

All clinical study treatment will be returned to Cougar or its representative or destroyed at the site as specified in writing by Cougar.

6 STUDY PROCEDURES

6.1 Informed Consent

Written Informed Consent and Authorization must be obtained from the patient in accordance with local practice and regulations. This study includes two informed consents: One main study informed consent form and a second optional molecular research informed consent form.

The study will be discussed with the patient, and a patient wishing to participate must give informed consent and Authorization for Use and Release of Health and Research Study Information (United States only) or Data Protection Consent (Europe only) prior to any study-related procedures or change in treatment.

A signed, Institutional Review Board/Ethics Committee (IRB/IEC) approved, informed consent must be obtained from patients before any study specific procedures or randomization can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record.

A copy of the fully signed informed consents will be given to the patient.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then evaluations should overlap (i.e., examine the patient together and discuss findings) for at least one visit.

Physical examination includes HEENT (head, eyes, ears, nose, and throat), chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations. Weight will be recorded at every visit. Height will be recorded at screening visit only.

Vital signs include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature. Weight will be recorded at every visit. Height will be recorded at screening visit only.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count with differential
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Coagulation Factors:

- Prothrombin Time (PT)
- Partial Thromboplastin Time (PPT)
- International Normalized Ratio (INR)

Urinalysis dipstick for:

- Blood
- Protein
- Glucose

(Microscopic examination if abnormal)

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Amylase
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Glucose
- Lactate dehydrogenase (LDH)
- Magnesium
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Total protein
- Uric acid

Serum Lipids (Cholesterol, HDL, LDL, triglycerides)

Additional laboratory tests:

- Prostate specific antigen (PSA) *
- Serum testosterone and other androgens (DHEA-S and steroid metabolites)*
- Pharmacokinetics (PK) *
- Circulating Tumor Cells (CTCs) *

Molecular characterization in CTCs**.

*Blinding will be maintained by not reporting post-treatment values of testosterone, steroid metabolites, PK, and CTCs to the Investigators or patients. Screening testosterone value will be reported to investigators to confirm patient eligibility

** Molecular characterization of CTCs will be optional and performed at selected specialized laboratories

6.4.2 Circulating Tumor Cell (CTC) Assessments

Circulating Tumor Cells (CTCs) enumeration will be processed using Veridex CellSearch™ platform. Blood samples will be collected at select study centers for a total of 6 blood samples drawn over 6 study visits for each patient enrolled. Two baseline samples will be collected; one at screening and one Cycle 1 Day 1 (if only one pre-dose visit takes place, then only one baseline sample will be collected). Subsequent samples will be collected at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 and at time of disease progression or discontinuation of study treatment visit. Samples will be shipped according to specified specialized laboratories referenced in the Laboratory Manual.

6.4.3 Pharmacokinetics (PK) Assessments and Additional ECG Monitoring

Pharmacokinetic and additional ECG assessments will be performed on approximately 150-200 patients at selected study centers. A total of 7 blood samples will be drawn over 3 study visits for each patient enrolled at these study sites. On Cycle 1 Day 1 (PK Visit 1), one blood sample will be taken at pre-dosing and two samples will be taken between 0.5 to 4 hours post-dosing. ECG will be collected at approximately 2 hours post-dose on Cycle 1 Day 1. At least 30 minutes should elapse between the two PK samples during post-dosing collection. Each patient will be asked to recall the date and time of the most recent meal prior to this visit (PK Visit 1). On Cycle 2 Day 1 and Cycle 5 Day 1 (PK Visit 2 and 3), patients will be instructed to withhold their scheduled morning dose. A blood sample will be collected prior to dosing and at 0-3 hours post-dosing. These two samples should be drawn at least 30 minutes apart. For PK Visit 2 and 3, each patient should be asked to recall: the date and time of his most recent dose of study medication prior to the dose given at the clinic and time of the meal preceding the dose at the clinic. The reason for collecting at Cycle 5, Day 1 (PK Visit 3) is to ensure information was collected at steady-state after longer term exposure to study treatment. Samples will be shipped to specified specialized laboratories referenced in the Laboratory Manual.

The table below provides a summary of the PK sampling scheme.

Visit/ Time	**PK Visit 1[a]** Cycle 1, Day 1			**PK Visit 2/PK Visit 3[b]** Cycle 2, Day 1 /, Cycle 5, Day 1	
Sample	1st	2nd	3rd	1st	2nd
Window (hr)[c]	-1 – 0[d]	0.5 – 2	2 – 4	-1 – 0	0 – 3

[a]Patients asked to recall most recent meal dates and times prior to administered dose.
[b]Patients asked to recall dates and times of most recent dose taken prior to clinic visit and most recent meal date and time preceding the dose administered at the clinic.
[c]Sampling time windows specified are relative to clinically administered doses.
[d]Sample to be taken prior to initial blinded dose of study medication.

6.4.4 Sample Collection, Storage, and Shipping

A Central Laboratory will analyze all hematology, blood chemistry, and urine samples collected for the study. Samples will be analyzed at a facility meeting Good Laboratory

Practice (GLP) requirements and/or using methods documented in a methods validation report. For sites participating in either pharmacokinetic and/or CTC enumerations or molecular research (separate ICF must be signed for CTC molecular research), samples will be shipped to and processed at a separate specialized laboratories.

6.5 Efficacy Assessments

6.5.1 The Primary Endpoint Measure

The primary endpoint of overall survival will be measured from date of randomization to death from any cause.

6.5.2 Secondary Endpoint Measures

- Post-treatment PSA level will be used to measure PSA response rate and time to PSA progression.
- PFS based on imaging studies

6.6 Other Measures

- Modified RECIST criteria will be used to assess objective tumor response.
- The Brief Pain Inventory-Short Form (BPI-SF) and analgesic usage score will be used to measure time to pain progression and proportion of patients experiencing pain palliation.
- Time to first skeletal-related events will be measured by the time to a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.
- Modified PFS based on criteria for discontinuation of treatment
- CTC enumeration
- Quality of Life questionnaire (FACT-P)
- Brief Fatigue Inventory (BFI)
- Medical resource utilization information
  - Hospital admission date
  - Hospital discharge date
  - Total number of days in the Intensive Care Unit
  - Principal reason for hospitalization
- Pharmacokinetics

6.7 Adverse Events Assessments

6.7.1 Safety Measures

All study patients who have received any dose of abiraterone acetate will be evaluable for safety.

- Adverse events including laboratory adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Appendix 5)
- Electrocardiograms (ECGs) and measurement of cardiac ejection fraction
- Laboratory tests (CBC with differential, coagulation factors, platelets, chemistry, urinalysis, and serum lipids)
- Vital Signs (oral or aural temperature, upright blood pressure, heart rate, respiratory rate and weight)
- Physical exam
- ECOG performance status

6.7.2 Definitions of an Adverse Event and Adverse Reaction

An adverse event (AE) is any reaction, side effect, or other untoward medical occurrence, regardless of relationship to study drug that occurs any time from the beginning of the first study dose administration in cycle 1 until the final study visit or early termination visit. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory test finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An adverse reaction (AR) is any untoward and unintended response to an investigational medicinal product related to any dose administered.

6.7.3 Clinical Laboratory Adverse Events

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the Cougar Medical Monitor (or his/her designated representative), or until a diagnosis that explains them is made. The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE), and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a SAE, and/or
5. Test result is considered to be an adverse event by the investigator or sponsor.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for Condition 4. Clinically significant laboratory results must be recorded in the patient's CRF.

6.7.4 Reporting of an Adverse Event

Throughout the course of the study, all AEs should be monitored and reported to Cougar or Cougar representative by the investigator or study personnel through the planned Adverse Event Reporting Process, including seriousness, severity, action taken and relationship to study drug. If adverse events occur, the first concern will be the safety of the study participants.

All ARs that are unexpected (not already listed as treatment related in the current Clinical Investigator's Brochure) are to be reported to the governing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

6.7.5 Definition of Serious Adverse Events or Reactions

A serious adverse event (SAE) or serious adverse reactions (SAR, a SAE related to investigational drug) is defined by ICH as any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.7.6 Reporting Serious Adverse Reactions (SAR)

Any expected or unexpected SAR, (unexpected from the perspective of previously observed and reported in the current Investigator’s Brochure (IB), not on the basis of what might be anticipated from the pharmacological properties of the medicinal product) occurring during the study period should be immediately reported (within 24 hours or 1 working day) to a Cougar representative listed on the Cougar personnel page and recorded on the appropriate case report form (CRF). All SAEs and suspected unexpected SARs (SUSARs) are to be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities, in compliance with GCP 4.11 Safety Reporting, as per European Directive 2001/20/EC as well as US Code of Federal Regulations 21 § 312.32 using a CIOMS-1 or MEDWATCH form.

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to investigational product will be collected and reported within 1 working day of discovery or notification of the event.

All Patients with a SAE that is related to investigational drug (a SAR) must be followed up and the outcomes reported. The investigator should supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

In the event of a SAE or SAR, the investigator must:

1. Notify Cougar representatives within 24 hours or 1 working day. Sites should contact the sponsor directly via a dedicated SAE contact number (global phone number will be provided).
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Cougar with a complete, written case history (adverse event report form) which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Ensure all AE and SAE reports are supported by documentation in the patient's medical records.
5. Notify local IRB/IEC, as per local requirements for reporting of SAEs. A copy of the IRB/IEC notification must be maintained at the site.

6.7.7 Suspected Unexpected Serious Adverse Reactions (SUSARS) And Reporting Requirements

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Cougar to be unlikely, possibly, or related to the study drug administered. Additional information on assessment of expectedness of a serious adverse event (SAE) is provided in the current IB.

When an SAE is judged reportable on an expedited basis, the event will be assessed for seriousness, expectedness and causal relationship as if it was the tested study drug that caused the reaction. If the event is unexpected and serious then it will be deemed to be a SUSAR and will be reported as a blinded SUSAR in order to maintain the blind and protect the integrity of the clinical investigation.

Regulatory authorities, central IRBs/IECs will be notified of the event(s) in accordance with local laws and regulations as well as the IDMC per this protocol (refer to Section 10.9 for IDMC function).

Since a fatal outcome (death) is the primary efficacy endpoint for this study, death events will not be unblinded in order to protect the integrity of the clinical investigation.

For all EU countries and Australia, only sudden and unexpected deaths will be treated as SUSARs and reported to the Competent Authority as detailed above.

For the US and Canada, all deaths will be treated as SUSARs and reported to the respective Health Authority as detailed above.

6.7.8 Timing of Adverse and Serious Adverse Events

Any AE and SAE experienced by the patient from Screening (serious pre-treatment events only) to Cycle 1 Day 1 and up to 30 days after the last dose will be documented. These events will be evaluated to determine the causal relationship with study treatment. Follow-up could be conducted by site via telephone attempts.

6.7.9 Severity of Adverse and Serious Adverse Events

Adverse event (AE) severity is a clinical determination of the intensity of an AE and SAEs. The severity assessment for a clinical AE should be completed using the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Any AE not listed in the CTCAE will be graded as follows:

SEVERITY OF EVENT	
Grade	Definition
1	Mild adverse event.
2	Moderate adverse event.
3	Severe and undesirable adverse event.
4	Life-threatening or disabling adverse event.
5	Death related to adverse event.

6.7.10 Relationship to Study Drug

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the study drug.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study drug:

RELATIONSHIP OF EVENT TO STUDY DRUG	
Unrelated	Any event that does not follow a reasonable temporal sequence from administration of study drug *AND* that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Unlikely	Any event that does not follow a reasonable temporal sequence from administration of study drug *OR* that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Possibly	Any reaction that follows a reasonable temporal sequence from administration of study drug *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

Related	Any reaction that follows a reasonable temporal sequence from administration of study drug *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

6.7.11 Management of Study Drug-Related Events

Based upon experience from Phase 1 and ongoing Phase 2 studies, abiraterone acetate is generally well tolerated. The most common adverse events related to abiraterone acetate monotherapy include fatigue due to reduced cortisol level as a result of CYP17 inhibition; and hypertension, fluid retention, and hypokalemia due to mineralocorticoid excess caused by compensatory ACTH drive. In this study, the concomitant administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive.

In this study, it is expected that significant portion of patients would have received corticosteroids for extended duration before study entry. During study, corticosteroid treatment will be continued. It has been documented that following prolonged therapy with corticosteroids, patients may develop Cushings syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without evidence of adrenal insufficiency.

For guidance on management of side effects of glucocorticoid usage, symptoms related to castration (androgen deprivation), severe and refractory headaches, fatigue, or other toxicities please contact the Medical Monitor.

Re-initiation of study medication treatment after resolution of adverse events must be discussed with and approved by the Protocol Medical Monitor.

6.7.11.1 Management of Hypokalemia

At the initial observation of Grade 1 hypokalemia (serum potassium < 3.5 mM or below lower limit of normal range, but ≥ 3.0 mM), oral potassium supplement will be initiated. The dose of potassium supplement must be carefully titrated to maintain serum potassium at ≥ 3.5 mM but ≤ 5.0 mM. Any patient with low potassium while on study or a history of hypokalemia from a pre-existing or concurrent medical condition will undergo weekly or more frequent laboratory electrolyte evaluation. The investigator should consider maintaining the patient's potassium level at ≥ 4.0 mM in these patients.

If any patient experiences Grade 3 hypokalemia (serum potassium levels < 3.0 mM – 2.5 mM, NCI CTCAE v3.0) or life-threatening hypokalemia with potassium levels < 2.5 mM (NCI CTCAE v3.0 hypokalemia Grade 4), abiraterone acetate treatment will be withheld, and the patient hospitalized for intravenous potassium replacement and cardiac monitoring.

Re-initiation of abiraterone acetate treatment after normalization of potassium levels must be discussed with and approved by the Protocol Medical Monitor.

Table 2. Hypokalemia Management

Serum K+	Grade of Hypokalemia	Action	Further Action and/or Maintenance
Low K+ and/or history of Hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations	Titrate dose to maintain a Serum K+ ≥3.5mM ≤5.0mM (Maintenance of pts at ≥ 4.0mM is recommended)
< 3.5mM – 3.0mM	Grade 1	Initiate oral K+ supplementation	Titrate dose to maintain a Serum K+ ≥3.5mM ≤5.0mM (Maintenance of pts at ≥ 4.0mM is recommended)
< 3.0mM – 2.5mM	Grade 3	Withhold Abiraterone Acetate (study) treatment and initiate IV K+ and cardiac monitoring	Call Cougar Biotechnology prior to re-initiating study treatment
< 2.5mM	Grade 4	Withhold Abiraterone Acetate (study) treatment and initiate IV K+ and cardiac monitoring	Call Cougar Biotechnology prior to re-initiating study treatment

6.7.11.2 Management of Hypertension Side Effects

- Grade 1-2–Management per Investigator. No study medication dose reduction.

- Grade 3-4 – Hold study medication. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When hypertension resolves to ≤Grade 1, resume study medication at full dose.

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

- If toxicity recurs despite optimal medical management and two dose level reductions, discontinue study medication.

6.7.11.3 Management of Edema, Fluid Retention

- Pedal edema - Supportive management per Investigator. No Study medication dose reduction

- Anasarca and/or Pulmonary edema requiring supplemental oxygen – Hold study medication. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When toxicity resolves to ≤Grade 1, resume study medication at full dose.

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

- If toxicity recurs despite optimal medical management and two dose level reductions, discontinue study medication

6.7.11.4 Management of Abnormal Liver Function Tests

- If Grade 1 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN): The frequency of liver function test monitoring should be increased, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.

- If Grade 2 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN): The frequency of liver function test monitoring should be increased to ≥ once a week, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.

- If Grade 3 or higher increases in AST, ALT, or bilirubin occur (e.g. increase in AST or ALT to >5X ULN; increase in total bilirubin to >3X ULN), hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If study treatment resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, and the Medical Monitor agrees, resume study treatment with the first dose level reduction (3 tablets, 750 mg of study treatment) when Grade 3 toxicities resolve to Grade 1 or baseline.

- If Grade 3 or higher increases in AST, ALT, or bilirubin recur after the first dose reduction hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If study treatment resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, and the Medical Monitor agrees, resume study treatment with the second dose level reduction (2 tablets, 500 mg of study treatment) when AST, ALT, or bilirubin returns to baseline value or Grade 1.

- If Grade 4 increases in AST, ALT, or bilirubin occur (e.g. increase in AST or ALT to >20X ULN; increase in total bilirubin to >10X ULN), patients must discontinue study treatment immediately and will not be rechallenged. They should be followed until resolution of abnormal liver function tests.

6.7.11.5 Management of Other Non-mineralocorticoid Based Side Effects

- If Grade 1-2 toxicities, give supportive care per institutional guidelines. No study medication dose reduction.

- If Grade 3 or higher toxicities, including headache (interferes with ADL), nausea (TPN, IVF), vomiting (>6 episodes/24hrs, TPN or IVF), diarrhea (IVF, hospitalization, hemodynamic collapse), or any other toxicity judged related to study treatment is observed where the patients safety is jeopardized, hold study medication.

- When toxicity resolves to ≤ Grade 1, resume study medication at full dose.

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

- If toxicity recurs despite aggressive medical management and two dose level reductions, discontinue study medication.

6.7.12 Dose-Reduction Procedure for Adverse Event Management

In the event where dose-reduction is considered to be due to an adverse reaction, 2 dose reductions are allowed. At each dose reduction, one tablet will be removed, e.g., 4→3 tablets, and 3→2 tablets. Otherwise AEs, although anticipated in this study, are primarily related to underlying advanced prostate cancer and its management; therefore, approaches other than dose reduction are recommended to manage the AE. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and a discussion with the Medical Monitor.

6.7.13 Serious Pre-Treatment Events

A serious pre-treatment event is defined as an event experienced by the patient after signing the informed consent form, but before administration of study treatment. These events are to be recorded on the Serious Pre-Treatment Event CRF and reported to the Medical Monitor within 24 hours of the study staff becoming aware of the event.

6.7.14 Treatment-Emergent Adverse Events

Treatment-emergent adverse events are those events that occur or worsen on or after first dose of abiraterone acetate/placebo up through 30 days post last dose of study treatment (abiraterone acetate or placebo), and/or any treatment-related adverse event, regardless of the onset date.

6.7.15 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized, provided the site stipulates the following:

- The prescheduled elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study.
- The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the patient's Cycle 1 Day 1 dosing in the study and the time of the procedure or treatment.
- The prescheduled elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

6.7.16 Long-Term Follow-Up

Patients who are no longer continuing with scheduled study visits will be followed for study-related SAEs or until the patient starts a subsequent therapy for prostrate cancer. Thereafter, the event should only be recorded if the Investigator considers it possibly related or related to study treatment.

6.8 Criteria for Discontinuation of Study Treatment

Consistent with the rationale for continuation of LHRH analogues after the development of metastatic CRPC, we hypothesize that prostate cancer cells that are growth arrested following treatment with abiraterone acetate are likely to resume proliferating when the drug is discontinued and that continued abiraterone acetate therapy may potentially slow down the progression of disease in a subpopulation of tumor cells that retain sensitivity to androgen deprivation.

Based on this consideration, Study Treatment will be continued until both radiographic and PSA progression has occurred, accompanied by signs of clinical progression such as pain progression or skeletal related events or if the treating physician decides to initiate new systemic anti-cancer therapy. The intent of these criteria is to maintain Study Treatment for patients with asymptomatic radiographic or PSA progression, given the absence of approved agents or alternative treatment options available for protocol participants who have failed both castration and chemotherapy.

To discontinue Study Treatment, all three of the following criteria are required:

1) PSA progression as defined by PSAWG eligibility criteria (25% increase over baseline) with minimum PSA increase of 5 ng/mL

2) Radiographic progression defined by at least one of the following:
   - Progression on bone scans with ≥ 2 new lesions not consistent with tumor flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥1 additional new lesion.
   - Soft tissue disease progression by modified RECIST criteria (baseline LN size must be ≥ 2.0 cm to be considered target or evaluable lesion)

3) Symptomatic or clinical progression defined by one of the following:
   - Pain progression - Worsening of pain due to metastatic bone disease defined as an increase of ≥ 30% in the worst pain over the past 24 hours on the BPI-SF numeric rating scale observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥ 30% observed at 2 consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4
   - Development of a skeletal related event (SRE) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone
   - Any increase in prednisone or prednisolone dose or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain is considered a disease progression event
   - Treating physician decides to initiate new systemic anti-cancer therapy

6.8.1 Criteria for Discontinuation of Study Treatment after Interim Analysis

Study treatment will continue until disease progression as determined by the investigator or when one of the criteria for withdrawal from study in Section 6.9 is met.

6.9 Withdrawal from Study

The investigator may withdraw a patient from study treatment phase for any of the following reasons. When possible attempts to collect overall survival should be made as specified in Section 7.3.

- Discontinuation of treatment criteria as defined in Section 6.8
- Dosing noncompliance: Study treatment administration and dosing compliance will be assessed on Cycle 1 Day 15 visit. A count of study treatment will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the protocol. Subsequent dosing compliance procedure will be conducted at each study visit. If a patient misses 14 or more doses within a single 28-day cycle, the patient should be discontinued from the study treatment Phase. All End-of-Study treatment procedures should be followed. The patient will be followed for survival.
- Sustained Side Effects: Patients who have sustained toxicities, such as hyperglycemia or hypertension that do not return to NCI CTCAE (version 3.0) Grade 1 or less with appropriate medical management, should be discontinued from the study treatment Phase. All End-of-Study treatment procedures should be conducted. The patient will be followed for survival.
- Initiation of new anticancer treatment: Patients will be discontinued from the protocol treatment when investigator, in his or her judgment, determines new treatment for prostate cancer is warranted. All End-of-Study treatment procedures should be conducted and the patient should be followed for survival.
- Administration of prohibited medications: The patient will be discontinued from the protocol treatment when prohibited drug is administered. All End-of-Study treatment procedures should be conducted and the patient should be followed for survival. Supportive care medications are permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded. The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment Phase. Use of other investigational drug therapy for any reason is prohibited.
- Patient withdraws consent. In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes follow-up phase for overall survival data collection. A patient's decision to take part in the study is voluntary and he may choose not to take part in the study or to stop taking part at anytime. If he chooses not to take part or to stop at anytime, it will not affect his future medical care or medical benefits.

7 STUDY ACTIVITIES

After unblinding at Interim Analysis, all patients will follow the schedule of events in Section 3.1.7.4. Therefore, section 7 will no longer be applicable.

7.1 Screening Period (Days –14 to Day 1)

The following activities/procedures will be conducted during the screening period which may occur over 14 days:

- Medical history including prior prostate cancer therapies, PSA, Stage, and Gleason score at diagnosis
  - Previous hormonal, cytotoxic, and experimental treatments with start and stop dates
- Demographics
- Pain (BPI-SF) and Analgesic Usage Score
- Fatigue (BFI) Inventory
- Physical examination, weight, and height
- 12 lead ECG
- MUGA (Multiple Gated Acquisition scan). Left ventricular ejection fraction (LVEF) must be greater then 50% for study eligibility. An ECHO (Echocardiogram) can be performed if MUGA is not possible.
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Laboratory tests:
  - CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
  - Coagulation studies (PT/PPT, INR)
  - Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, and magnesium.
  - Fasting glucose (overnight 8 hr. fast) can be collected as part of chemistry panel run by central lab when possible or as a pre-test run by site local laboratory if patient would be coming in not fasted. Local lab results will be collected on the supplemental lab CRF
  - Serum Lipids (Cholesterol, HDL, LDL, and triglycerides)
  - Urinalysis: routine dipstick.
  - PSA: If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE.
  - Serum testosterone, and other androgen measurements (DHEA-sulfate and steroid metabolites); please note that a local lab serum testosterone should be sent to confirm eligibility. The central laboratory sample should also be submitted.
  - CTC blood collection for enumeration and optional molecular characterization
- Baseline tumor assessment:

- CT, MRI, or other imaging procedures as defined in Appendix 4: Tumor burden must be evaluated by physical examination and image-based evaluation (modified RECIST criteria). Baseline assessments should include CT or MRI of chest, abdomen and pelvis (ultrasound should not be used to measure lesions that are not clinically accessible, such as liver lesions).
- Chest X-ray: If a Chest CT or MRI is performed as part of the imaging evaluation, then the chest X-ray is optional and may not be performed.
- Bone Scan
- *Scans performed up to 28 days prior to Cycle 1 Day 1 can be used for baseline assessments.*

- Concomitant medications listing
  - Obtain a complete and thorough listing of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.

7.2 Treatment Period (Cycle 1 Day 1 to Termination of Treatment)

7.2.1 Cycle 1 Day 1

Patients who are eligible will be randomized and start study treatment within 14 days after the screening visit.

Cycle 1 Day 1 visit may occur on the same day as the Screening visit provided that all screening assessments have been completed and screenings results are reviewed prior to the commencement of Cycle 1 Day 1 assessments. In the event that Screening and Cycle 1 Day 1 visits are <3 days apart, Cycle 1 Day 1 assessment does not need to be repeated, except for the vitals and serum potassium, if it has already been conducted as part of the screening assessment.

The following procedures should be carried out prior to dosing of study treatment:

- Update listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4) with any event that may have occurred since screening
- Pain (BPI-SF) and Analgesic Usage Score
- Fatigue (BFI) Inventory
- Quality of Life (FACT-P)
- Concomitant Medications listing
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Laboratory tests
  - CBC: WBC, RBC, hemoglobin, hematocrit, platelets with differential count
  - Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, and magnesium

- PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Coagulation studies (PT/PPT, INR)
- CTC blood collection for enumeration and optional molecular characterization

PK Assessment for Patients at Selected Study Centers Only:

- PK pre-dose sample (up to 1 hour prior to on-site study dose administration)

Dosing of study treatment:

- Collect date and time of most recent meal patient had prior to providing study treatment.
- Administer study treatment and collect time

The following procedures should be carried out following dosing of study treatment:

- Collect PK sample between 0.5 and 2 hours post-dose
- 12 lead ECG at approximately 2 hours post-dose
- Collect PK sample between 2 and 4 hours post-dose (must be collected at least 30 minutes apart from first post-dose sample)
- AE evaluation and recording

7.2.2 Cycle 1 Day 15 Visit

The following assessments should be carried out at 14 days post-dose visit on Day 15:

- Pain (BPI-SF) and Analgesic Usage Score
- Fatigue (BFI) Inventory
- Physical examination and weight
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Laboratory tests
- Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, magnesium
- Coagulation studies (PT/PPT, INR)
- Concomitant Medications listing
- AE evaluation and recording will be monitored throughout the study. At each post baseline visit, the investigator will begin by querying for adverse events by asking each patient a general, nondirected question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate.
- Dosing compliance check, a count of study treatment tablets, will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re instructed regarding proper dosing procedures and may continue in the protocol. Source documentation of the compliance check and any patient verbal re-instruction provided should be documented in patient's chart.

7.2.3 Cycles 2, 3, 5, 6, 8, 9, 11, and 12 Day 1 (Continue every 1st and 2nd cycle Beyond Cycle 12)

The following assessments should be carried out at the indicated time point:

- Pain (BPI-SF) and Analgesic Usage Score
- Fatigue (BFI) Inventory
- Physical examination and weight
- Vital signs including upright blood pressures, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Concomitant medications listing
- AE evaluation and recording
- Disease progression assessment
- Dosing compliance check, a count of study treatment tablets, will be conducted during this visit and patient dosing compliance will be assessed. If compliance is ≤ 75% patient should be re-instructed regarding proper dosing procedures. Patients whose dosing compliance is ≤ 75% for 2 consecutive cycles should be discontinued from the study. Patients who have a compliance ≤ 75% secondary to held doses due to toxicities as described in Section 6.7.12 may continue in the study. Source documentation of the compliance check and any patient verbal re-instruction provided should be documented in patient's chart.
- Laboratory Tests:
  - CBC: WBC, RBC, hemoglobin, hematocrit, platelets with differential count
  - Coagulation studies (PT/PPT, INR)
  - Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, magnesium
  - CTC blood collection for enumeration and optional molecular characterization (Cycles 2 and 3 only)

PK Assessment for Selected Study Centers (Cycles 2 and 5 only):

- PK pre-dose sample (up to 1 hour prior to on-site study dose administration)

Dosing of study treatment:

- Collect date and time of most recent study treatment prior to the study visit. Collect date and time of most recent meal patient had prior to providing study treatment.
- Administer study treatment and collect time

The following procedures should be carried out following dosing of study treatment:

- Collect PK sample between 0 and 3 hours post-dose

7.2.4 Cycle 2 Day 15 and Cycle 3 Day 15 Visit

The following assessments should be carried out at 14 days post-dose visit on Day 15:

- Laboratory Tests:
  - Chemistry (Liver Function Test): AST, ALT, alkaline phosphatase, total bilirubin

7.2.5 Cycles 4, 7, and 10 (continue every 3rd cycle beyond Cycle 10) and Treatment Discontinuation Visit

In preparation for the study visit, the following assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycle 4, 7, or 10 Day-1 visit and any visit when treatment is discontinued.

- CT, MRI, or other imaging procedures as defined in Appendix 4 (Cycle 4, 7 or 10 Day 1 Visit)
  - Chest X-ray: If a Chest CT or MRI is performed as part of the imaging evaluation, then the Chest X-ray is optional and may not be performed
- Bone Scan or other imaging procedures
- Multiple Gated Acquisition scan (MUGA) in patients who have received prior mitoxantrone only. An ECHO (Echocardiogram) can be performed if MUGA is not possible. If MUGA is performed, ECG can be collected during MUGA instead of during actual study visit.

At the study visit the following assessments should be conducted:

- Pain (BPI-SF) and Analgesic Usage Score
- Fatigue (BFI) Inventory
- Quality of Life (FACT-P) (After Cycle 10, QOL assessment will be collected every 6 cycles up to the Treatment Discontinuation Visit)
- Physical examination and weight
- 12-lead ECG
- Vital signs including upright blood pressures, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Laboratory Tests
  - CBC: WBC, RBC, hemoglobin, hematocrit, platelets with differential count
  - Coagulation studies (PT/PPT, INR)
  - Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, magnesium
  - Fasting glucose (overnight 8 hr. fast) can be collected as part of chemistry panel run by central lab when possible or as a pre-test run by site local laboratory if patient would be coming in not fasted. Local lab results will be collected on the supplemental lab CRF
  - Serum Lipids (Cholesterol, HDL, LDL)
  - Serum testosterone, and other androgen measurements (DHEA-sulfate and steroid metabolites)
  - PSA: If patient undergoes a DRE, then PSA must be sampled prior to the DRE.

  - CTC blood collection for enumeration and optional molecular characterization (Cycle 4 and at disease progression)
- Concomitant medications listing
- AE evaluation and recording
- Disease progression assessment
- Dosing compliance check. If Treatment Discontinuation Visit then a count of study drug tablets will be conducted and final patient dosing compliance will be assessed.

7.2.6 End-of-Study Visit

The following safety assessments should be carried out at the End-of-Study participation when patients are off study or terminate early:

- Physical examination and weight
- Vital signs including upright blood pressures, heart rate, respiratory rate, and oral or aural body temperature.
- Assessment of ECOG Performance Status
- 12-lead ECG
- MUGA (Multiple Gated Acquisition scan). An ECHO (Echocardiogram) can be performed if MUGA is not possible.
- Laboratory tests
  - CBC: WBC, RBC, hemoglobin, hematocrit, platelets with differential count
  - Coagulation studies (PT/PPT, INR)
  - Chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, magnesium.
  - Fasting glucose (can be collected as part of chemistry panel run by central lab when possible or as a pre-test run by site local laboratory if patient would be coming in not fasted. Local lab results will be collected on the supplemental lab CRF)
  - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
  - Serum Lipids (Cholesterol, HDL, LDL)
  - CTC blood collection for enumeration and optional molecular characterization (if not obtained at time of disease progression or treatment discontinuation visit)
- Concomitant medications listing
- Adverse events
  - AE follow-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists is required for 30 days post last dose or until patient receives anticancer therapy, whichever comes first. Follow-up could be conducted by site via telephone attempts. The attempts and outcomes should be recorded as part of the patient source documents.
- Final Dosing compliance check if not performed at the Treatment Discontinuation Visit.

7.3 Post-Treatment Follow-up Period (Survival or Long-Term Follow-Up)

Once a patient has completed the study, progressed or started another anticancer therapy, overall survival follow-up should be performed every 3 months for up to 60 months (5 years). Overall Survival may be collected by telephone interview or chart review.

8 QUALITY CONTROL AND ASSURANCE

During and/or after completion of the study, quality assurance auditor (s) named by Cougar or the regulatory authorities may wish to perform on-site audits. The investigators will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

Cougar representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Cougar's Quality Assurance Department (or designees). Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH Good Clinical Practice (ICH E6), US Investigational Drugs (21CFR312), EU Clinical Trials Directive (Directive 2001/20/EC), and applicable regional regulatory requirements.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All statistical analyses will be performed using SAS®. The resulting statistic will be evaluated using East® given the precise number of events observed at the time of interim analysis.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

9.2 Determination of Sample Size

This is a group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method. One interim analysis and one final analysis are planned (East®). The interim and final analyses of data will be performed after the pre-specified number of death events are observed (see Sections 9.3 to 9.9 below). All statistical tests of treatment effects will be conducted at the two-sided 0.05 level of significance.

Patients will be randomized in a 2:1 ratio to receive abiraterone acetate plus prednisone or placebo plus prednisone. Patients with metastatic CRPC after failure of docetaxel-based chemotherapy are expected to have an estimated median overall survival of 12 months. It is assumed that failure will follow an exponential distribution with a constant hazard rate. The planned sample size of approximately 1158 patients (772 on abiraterone acetate and 386 on placebo) will provide 85% power to detect a difference between a median survival of 15 months in the abiraterone acetate group and a median survival of 12 months in the placebo group (hazard ratio=0.80) under the assumptions of a 2-tailed significance level of 0.05 and an enrollment of approximately 13 months over a total duration of approximately 30 months to obtain the required 797 total events.

9.3 Analysis Populations

Patient disposition and efficacy analyses will be performed on data from the intent-to-treat (ITT) population. All randomized patients will be included in the ITT analysis who will be classified according to their assigned treatment group, regardless of the actual treatment received. The primary efficacy analyses will be on the ITT basis.

All patients who receive at least one dose of study drug will be included in the analysis of safety (Safety Population).

9.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics will include time from diagnosis, time since initiating chemotherapy to study drug, prior chemotherapy, and etc (as documented in the CRF) will be presented.

9.5 Study Endpoint(s)

9.5.1 Efficacy Endpoint(s)

9.5.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is OS, and will be measured from the date of randomization to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

9.5.1.2 Secondary Time to Event Endpoint

- PSA response is scored in patients achieving a post-treatment PSA decline of at least 50% according to the protocol-specific PSAWG criteria (Appendix 3).
- Time to PSA progression will be measured from the time interval from the date of randomization to the date of the PSA progression as defined in the protocol-specific PSAWG criteria (Appendix 3). The determination of PSA progression will require that the patient receive at least 3 cycles of therapy. A rise in PSA value alone, in the absence of radiographic progression, during the first 3 cycles will not be considered disease progression.
- Radiographic PFS will be measured from the date of randomization to the first occurrence of radiographic progression or death. Progression is defined as the time from randomization to the occurrence of either tumor progression in soft tissue according to modified RECIST criteria (Appendix 4: baseline lymph nodes $\geq$ 2 cm to be considered as target lesions) or by bone scan ($\geq$ 2 new lesions confirmed $\geq$ 6 weeks later shows $\geq$ 1 additional new lesion). If no event exists, then PFS will be censored at the last scheduled disease assessment on study. PFS of living patients with no assessment on-study, and PFS of patients with no baseline assessment will be censored at randomization.

9.5.1.3 Other Efficacy Endpoints

- Objective response is achieved in patients with a complete or partial response by modified RECIST criteria.
- Proportion of patients experiencing pain palliation using BPI-SF worst pain intensity score and analgesic score
- Time to pain progression will be measured from the date of randomization to the first observation of symptomatic pain progression.
- Time to first skeletal-related event will be measured from the date of randomization to the first observation of skeletal-related event, defined as pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. In the

absence of skeletal-related events, events will be censored at the last assessment in the study. Patients with no such assessment on-study will be censored at randomization.

- Modified PFS based on criteria for discontinuation of study treatment criteria from the date of randomization to death or the first observation composed of:
  1. PSA progression, and
  2. Radiographic progression, and
  3. Pain progression, SRE, increase in glucocorticoid use, or initiation of a new systemic anti-cancer therapy
- Proportion of patients achieving a decline in circulating tumor cells (CTCs)/7.5ml to less than 5
- QOL total score and each subscale score as assessed by FACT-P

Distribution of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. The median times to event with two-sided 95% confidence intervals will be estimated, together with the estimate of event rates at 6 and 12 months. Stratified logrank test will be used as the primary analysis for treatment comparison; the score statistic from the cox proportional hazards model will be used in the estimation of the hazard ratio and the associated 95% confidence interval will also be provided.

Response variables are the proportion of patients fulfilling the respective criteria for response. The relative risk (treatment: control) will be reported along with the associated 95% confidence interval. Statistical inference will be evaluated using Chi-square statistic; the Fisher's exact test may be used if the expected counts in some cells are small.

The total score and the subscale scores assessed by FACT-P for the QOL will be descriptively summarized and t-test will be used to compare the score at each time point with the baseline score. Repeated measures analysis may be carried out as appropriate.

In addition, non-stratified analyses and cox proportional analyses will also be carried out for the primary endpoint of OS as supportive analysis. Sensitivity and subgroup analyses will also be carried out as appropriate.

9.5.2 Safety Evaluations

Safety analysis will be summarized using the Safety Population.

Extent of exposure to study drug will be summarized and details will be provided.

Treatment emergent adverse events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be coded using the MedDRA coding system and all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE).

Incidence of AEs will be summarized by system organ class (SOC) and preferred term (PT), and will be presented by treatment groups and overall. Adverse events will be summarized

by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarized by treatment groups. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced.

Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term.

Clinical laboratory test results will be collected pretreatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

Mean change from baseline in laboratory test values at each visit will be provided. On-study clinical laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be summarized.

Electrocardiograms data will be descriptively summarized for QTc, PR interval, and QRS at each visit. Comparison between baseline and maximum on-study QTc will also be presented. Both Fredericia and Bazett corrections will be reported.

Multiple gated acquisition (MUGA)/echocardiogram (ECHO) scan data will be collected. Distribution of the results from MUGA and/or ECHO will be summarized in terms of number of patients and percentages of patients whose ejection fraction falls below 50%.

9.6 Pharmacokinetics Analysis

Approximately 150-200 patients are scheduled to be enrolled at selected sites for the PK assessment. Based on the 2:1 randomization this should yield approximately 100-133 patients on active treatment (abiraterone acetate).

Nonlinear mixed effects modeling will be used to develop a population PK model for abiraterone plasma concentrations in HRPC patients. A covariate analysis will be performed to investigate the influence of patient factors on the apparent clearance of abiraterone. Patient factors will include, but are not limited to, body weight, calculated creatinine clearance, liver function, sex, age, race, and time of meal relative to the time of dose administration. Patient factors on other disposition and absorption parameters will be tested in a secondary fashion. A separate report will be generated summarizing the results from the modeling.

9.7 Circulating Tumor Cells (CTC)

Change in CTC counts will be descriptively summarized. Analyses of proportion of CTC responder and its potential clinical benefit with respect to the primary endpoint will be carried out as described in Section 9.5.1.3. Analyses on CTC responders will also be presented by visit. Additional analyses to explore CTC enumeration as surrogate for clinical benefit will be provided in a separate report.

9.8 Other Assessments or Analyses

Other endpoints of the study are fatigue as evaluated in the Brief Fatigue Inventory (BFI) instrument, pain evaluated in the Brief Pain Inventory (BPI), and medical resource utilization (MRU) information. Descriptive statistics will be presented for each item collected.

In addition, analysis of pharmacoeconomic data and production of a final pharmacoeconomic report will be handled separately from the final clinical study report. Information obtained from the collection of medical resource utilization data may be combined with other data, such as cost data or other clinical parameters, in the production of final pharmacoeconomic report.

9.9 Interim Analysis

A group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method was used in the planning of the study (East®). In this study, there will be one interim analysis after 534 death events are observed (67% of 797 total events) and a final analysis after observing the required 797 total events. Details of the interim analysis and final analysis are provided in the table below.

Variable	**Interim Analysis**	**Final Analysis**
Number of Patients Enrolled	1158	1158
Number of Events	534	797
Efficacy Boundary (HR)	0.7975	0.8628
Cumulative Power	0.4864	0.8500
Cumulative Alpha Spent (2-tailed)	0.0124	0.0500

These stopping boundaries were calculated assuming that the number of events available at the time of interim analysis is exactly as planned and as provided in the above table. The actual stopping boundaries will be determined at time of analysis based on the number of events included in the analysis.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

10.1.1 Investigator Responsibilities

The investigator undertakes to perform the study in accordance with ICH Guidelines per Good Clinical Practice (GCP) and the applicable regulatory requirements. A copy of the guidelines will be available in the Investigator Site File.

It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The investigator should also be able to demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the investigator and sub-investigator(s) will be provided to Cougar (or its representative) before starting the study.

If the patient has a primary physician, the investigator should, with the patient's consent, inform them of the patient's participation in the study.

Agreement with the final clinical study report will be documented by the signed and dated signature of the principal or coordinating investigator in compliance with ICH E3.

10.1.2 Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria. The investigators will be required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

It is the investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study. In particular, the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/IEC must be informed of study completion.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

It is the responsibility of the investigator to submit this protocol, the final approved informed consent document (approved by Cougar or its representative), relevant supporting information, and all types of patient recruitment or advertisement information (approved by Cougar or its representative) to the IRB/IEC for review and it must be approved before the study is initiated. Prior to implementing changes in the study, Cougar will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

On the approval letter, the study (title, protocol number and version), the documents reviewed (protocol, informed consent material, amendments) and the date of review should be clearly stated.

Drug supplies will not be released and the patient recruitment will not begin until this written approval has been received by Cougar or its designee.

The investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once a year. The investigator must also keep the IRB/IEC informed of any serious and significant adverse events.

10.3 Ethical Conduct of the Study

This protocol accords with the principles of the Declaration of Helsinki as set forth at the 18th World Medicines Association (Helsinki 1964) and amendments of the 29th (Tokyo 1975), the 35th (Venice 1983), the 41st (Hong Kong 1989), the 48th, and the 52nd (Edinburgh 2000) World Medicines Association. As these accords are reviewed and amended periodically, the most current amended version will be in effect.

10.4 Patient Information and Consent

It is the responsibility of the investigator to obtain written informed consent from patients or patient's legal representative. Each patient is requested to sign the patient Information and Consent Form after the patient has received written information and an explanation of what the study involves, i.e., the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the Patient Information and signed Consent Form must be given to the patient. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

If the Independent Ethics Committee requires modification of this form, the documentation supporting this requirement must be provided to Cougar along with the new version. Cougar reserves the right to reject these modifications, should they not cover the minimum information required by ICH GCP.

10.5 Patient Confidentiality

Data collected during this study may be used to support the development, registration or marketing of abiraterone acetate. All data collected during the study will be controlled by Cougar or designee and Cougar will abide by all relevant data protection laws. After patients have consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of Cougar and/or the company organizing the research on Cougar's behalf to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may additionally be reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number. The results of this

study may be used in other countries throughout the world that have ensured an adequate level of protection for personal data.

Written Authorization (US sites only) or Data Protection Consent (European sites only) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ("EU Directive") and any other state and country privacy requirements). If the patient is under the legal age of consent, the Authorization (US sites only) or Data Protection form (European sites only) must be signed by the legally authorized representative in accordance with the applicable privacy requirements and other state and country privacy requirements.

10.6 Study Monitoring

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the US FDA, EMEA, other national authorities (ie, MHRA, BfArM), and local health authorities, Cougar and its representatives, and the IRB/EC for each study site. As a sponsor of this study, Cougar may delegate some administrative aspects of this study to a duly authorized representative including, but not limited to, study initiation, monitoring, and management of SAE reports.

Cougar or representative's monitor is responsible for verifying the eCRFs at regular intervals (approximately every 6-8 weeks) throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to the patients' medical records and other study-related records needed to verify the entries on the eCRFs.

10.7 Case Report Forms

Electronic Case Report Forms (eCRFs) will be provided by Cougar or its representative and should be handled in accordance with instructions from Cougar or its representative.

The investigator is responsible for maintaining adequate and accurate eCRFs which have been designed to record all observations and other data pertinent to the clinical investigation. Each eCRF should be filled out completely by the investigator or delegate as stated in the Site Delegation List. All data captured for the study is planned to be electronic. However, if necessary, data captured may be performed using paper CRFs.

If paper CRFs are used, then all CRFs should be completed in a neat legible manner to ensure accurate interpretation of the data; a black ball-point pen should be used to ensure the clarity of reproduced copies of all CRFs. Incorrect entries should be crossed with a single line. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary, by an authorized (investigator/co-worker) person. Overwriting of this information or use of liquid correcting fluid is not allowed.

The eCRFs should be reviewed, signed and dated by the investigator.

Once the site monitor has verified the contents of the completed eCRF pages against the source data, the EDC system will be locked for those pages. Queries may be raised if the data are unclear or contradictory, which must be addressed by the investigator.

10.8 Laboratory Assessments

A Central Laboratory and select specialty laboratories will be responsible to analyze safety labs collected for the study as well as some of the additional and speciality lab tests. Site local laboratories may be used to run fasting glucose, serum potassium prior to ECG, or repeat test when it is not possible to send samples to the central lab. All local laboratory results will be captured on supplemental lab eCRFs.

10.9 Independent Data Monitoring Committee (IDMC)

An external Independent Data Monitoring Committee (IDMC) will monitor and advise on interim safety and efficacy aspects of the study and relevance of new external information as specified in the IDMC charter. Key safety and efficacy (i.e. SAEs, SUSARs, deaths, etc) data will be provided to the IDMC with treatment groups randomly identified (from meeting to meeting) as either "X" or "Y". Treatment group identification may be obtained from the Independent Biostatistician if the IDMC determines that unblinding is necessary to determine whether the study should be stopped early for either safety or efficacy. Refer to the IDMC Charter for details.

10.10 Central Radiologic Review

All CT, MRI, and Bone scans will be collected centrally in the event of a retrospective independent review of radiographic progression (a secondary endpoint in this study).

10.11 Protocol Violations/Deviations

Protocol deviations should be reported to Cougar (or designee) as they occur or are discovered and should be captured in eCRFs at the time of monitoring and medical review of data line listings.

10.12 Access to Source Documentation

Source data to be reviewed and/or during this study will include, but is not restricted to: patient's medical file, patient's diary cards (if applicable), and original laboratory test, histology, and pathology reports.

All key data must be recorded in the patient's hospital notes.

The investigator will permit authorized representatives of Cougar, the respective national or local health authorities, and auditors to inspect facilities and records relevant to this study.

The monitor (auditors, IEC/IRB or regulatory inspectors) will check the CRF entries against the source documents. The consent form will include a statement by which the patients allow the monitor/auditor/inspector from the IEC/IRB or regulatory authority access to source data (eg, patient's medical file, appointment books, original laboratory test reports, X rays etc) that substantiate information in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal drug information.

10.13 Retention of Data

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, consent forms, laboratory test results, and drug inventory records, should be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Cougar. The investigator should obtain written permission from Cougar prior to the destruction of any study document.

These records should be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with 21 CFR 312.68 or other National Regulatory Authorities.

10.14 Financial Disclosure

The investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study following information; any significant payments of other sorts from Cougar, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in abiraterone acetate; any significant equity interest in Cougar as defined in the US Code of Federal Regulations (21 CFR 54 2(b)).

In consideration of participation in the study, Cougar will pay the investigator, or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

10.15 Study Publication Guidelines and Disclosure Policy

Cougar Biotechnology ("Sponsor") encourages publication of results derived from the clinical research it sponsors. *Publication* includes publication of a paper in a peer-reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting, or making results public by some other means. Sponsor will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-Chairs/Principal Investigator(s) is/are permitted to publish/present the results of the study, in part or in their entirety without the written authorization of Sponsor. The review is aimed at protecting Cougar's pre-existing propriety information and commercial interests

First Publication

The results of the entire multi-center study shall be presented in a first publication upon completion of the entire multi-center study (data lock), with authorship being determined by Sponsor and Study Co-Chairs using the criteria defined by the International Committee of Medical Journal Editors. At least 2 Sponsor representatives will also be included as coauthors on the first publication of the results of the entire multi-center study to allow recognition of the Sponsor's involvement in the design and execution of the study.

Subsequent Publications

Results from data subsets should not be published in advance of and must make reference to the first publication. Publications must include at least 2 Sponsor authors to allow recognition of the Sponsor's involvement.

In all publications, the study is to be identified as COU-AA-301. The Study Co-Chairs/Principal Investigator(s) shall be free to publish or present, subject to the timing described in the Clinical Trial Agreement.

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Appendix 1 Schedule of Events

Table of Scheduled Events

		Treatment Phase						Follow-Up Phase
Evaluation	**Screening Day -14 to 1**	**[1]Cycle 1 Day 1**	**Cycle 1 Day 15**	**[1] Cycle 2, 3, 5, 6, 8, 9, 11, 12 Day 1**	**Cycle 2 and 3 Day 15**	**[1]Cycle 4, 7, and 10 Day 1 and at Treatment Discontinuation[2]**	**End of Study Visit[3]**	**Q3 Months up to Month 60**
Procedures								
Signed consent form[4]	X							
Medical history, prior prostate therapies	X							
QOL - FACT-P		X				X[5]		
BPI-SF, analgesic usage	X	X	X	X		X		
BFI, Fatigue	X	X	X	X		X		
Physical exam and Weight[6]	X		X	X		X	X	
Vital signs[6]	X	X	X	X		X	X	
ECOG	X	X	X	X		X	X	
12 Lead ECG[7]	X					X	X	
MUGA Scan or Cardiac ECHO	X					X[8]	X	
Dosing compliance			X	X		X	X	
Concomitant medications	X	X	X	X		X	X	
Adverse events	X[9]	X	X	X		X	X[10]	
Laboratory Assessments								
CBC	X	X		X		X	X	
Coagulation Factors-PT/PTT (INR)	X	X	X	X		X	X	
Serum chemistry, electrolytes[18]	X	X	X	X	X	X	X	
Fasting Glucose[11]	X					X	X	
Serum Lipids	X					X	X	
PSA[12]	X	X				X	X	
Serum testosterone and other androgens	X					X		
Urinalysis (dipstick)	X							
CTC Assessments	X	X		X[13]		X[13]		
Tumor Assessments								
CT / MRI /other imaging procedure Chest x-ray[14]	X					X		
Bone Scan[14]	X					X[15]		
Disease progression assessment						X		
Overall survival								X[16]
PK[17] and Additional ECG Sampling at Select Study Centers								
Pre-dose PK		X		X[17]				
In Clinic Dosing of Study Treatment for PK[17]		X		X				
1st Post –dose PK		X		X[17]				

2 hr Post-Dose ECG[7]		X						
2nd Post –dose PK		X						

1 If patient's continues on study with out disease progression or discontinuation of treatment beyond Cycle 12 they should continue visit assessments as indicated for every 3rd Cycle starting with Cycle 13 and restart to every 1st and 2nd Cycle visit assessments following.

2 Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease is required.

3 End of Study Visit should be scheduled to collect safety assessments between 15 to 28 days after the patient stops treatment. Patients will enter Follow up Phase at that time.

4 Written informed consent must be obtained within 30 days prior to Cycle 1 Day 1.

5 After Cycle 10, QOL assessment will be collected every 6 cycles up to the Treatment Discontinuation Visit.

6 Weight will be recorded at every visit. Height will be measured at Screening visit only. Vitals Include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

7 An ECG should be obtained prior to Day 1 visit, every 3 cycles, and at End of Study visit except for patients in the PK sampling portion of the protocol who will also have ECGs collected at approximately 2 hrs post-dose on Cycle 1. ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.

8 A MUGA scan should be obtained at baseline and at End of Study visit in all patients. Patients who have had prior mitoxantrone should also have a MUGA scan at every 3 cycles. A cardiac ECHO can be used if MUGA is not available or when ECHO is standard of care at the study site.

9 Pre-Treatment SAEs should be reported from time patient signs a consent form up to Day 1 treatment administration.

10 Adverse event follow-up is required for 30 days following last dose to determine if any new or ongoing drug related AE or any SAE regardless of relationship to drug exists. Follow-up could be conducted by sites via telephone attempts and must be documented in source notes.

11 Fasting Glucose can be done as part of Chemistry Panel run by central laboratory when possible or as a pre-test run by site local laboratory to full chemistry panel if patient would be coming in not fasted. If local lab used results will be collected on the supplemental Lab CRF.

12 If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE

13 CTCs will be collected from select centers at screening, Cycle 1 Day 1, and then Cycle 2, 3, and 4 Day 1, and at time of disease progression. CTC enumeration will be run on all samples collected; molecular characterization will be performed on samples when patients provide a signed informed consent form for molecular testing.

14 *Scans (CT, MRI, and Bone) performed up to 28 days prior to Study Day 1 can be used for baseline assessments.* If a status of partial or complete response is made, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. If a Chest CT or MRI is performed as part of the imaging evaluation, then the Chest x-ray is optional and may not be performed.

15 Bone scans after screening should be conducted as part of the response assessment

16 Overall survival may be collected by telephone interview or chart review

17 *Selected Study Centers Only:* PK blood samples collected pre and post dose on Cycle 1 Day 1 (2 post dose samples on Cycle 1), Cycle 2, and Cycle 5. Patients will be asked to withhold their daily dose and take study treatment following pre-sample PK collection. Additional ECG assessments at approximately 2-hour post dose on Cycle 1.

18 At C2D15 and C3D15 Chemistry is limited to Liver Function Tests: AST, ALT, alkaline phosphatase, and total bilirubin

Appendix 2 Study Treatment Preparation and Dispensing Instructions

Labeling/Packaging

Study treatment (Abiraterone Acetate and placebo) will be provided to each site packaged for patient assignment at the time of randomization. Packaging includes a 30-day supply. Site pharmacist will dispense the study treatment to each patient in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure.

Storage of Study Treatments

The study treatment must be stored in a secure area and administered only to patients who entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

Investigational product should be stored at the study site at a room temperature between 15ºC to 30º C. Bottles of study drug should be stored with the cap on tightly and should not be refrigerated as this is a high relative humidity environment.

Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Cougar Biotechnology, Inc., dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Cougar Biotechnology, Inc. during and at the completion of the study. A detailed inventory must be completed for the study treatment. The study treatment must be dispensed only by an appropriately qualified person to patients in the study. The treatment is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

Return or Disposal of Study Medications/Treatments

All clinical study treatments will be returned to Cougar Biotechnology, Inc. or destroyed at the site as specified in writing by Cougar Biotechnology, Inc.

Destruction of study treatments at the site should be done in the presence of a Cougar Biotechnology, Inc. representative. Alternatively, destruction of the treatments may be carried out by a suitably qualified person based on written instructions from Cougar Biotechnology, Inc.

Appendix 3 Protocol-Specific Prostate-Specific Antigen Working Group Criteria

Progressive Disease after Androgen Deprivation Eligibility Criteria:

PSA evidence for progressive prostate cancer consists of a PSA level of at least 5 ng/ml that has risen on at least 2 successive occasions, at least 2 weeks apart. If the confirmatory PSA (Figure 13.1, #3) value is less (Figure 13.1, #3b) than the screening PSA (Figure 13.1, #2) value, then an additional test for rising PSA (#4) will be required to document progression.

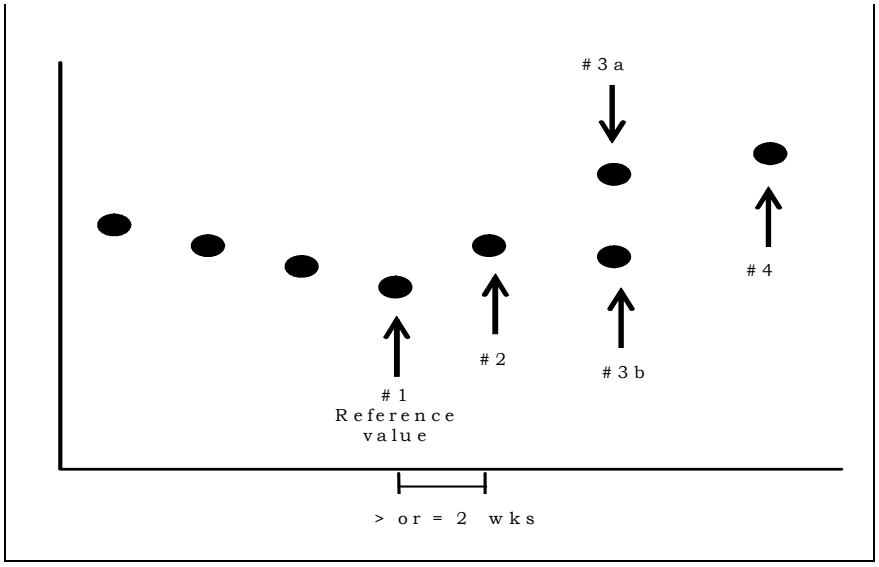


Figure 13.1: Eligibility Based on PSA

Procedures for Assessing PSA Progression Post Study Treatment:

PSA measurements will be per protocol post study treatment every 3 Cycles (e.g., Cycles 4, 7, 10,…). PSA increases and decreases will be tracked in order to assess disease response.

PSA partial response is defined by at least a 50% decline from screening (baseline) PSA value. The decline must be confirmed by a second PSA value collected at the time of the next scheduled imaging procedures for disease assessment (eg, Cycle 4, 7, 10, …).

PSA progressive disease may be defined in both patients who have not shown a decrease in their PSA and those who have. For patients who have not shown a decrease, progressive disease is defined as an increase of 25% over the screening (baseline) PSA value and in increase in the absolute-value PSA level by at least 5ng/mL. This increase should be confirmed by a second value.

For those patients whose PSA have decreased but has not reached response criteria, progressive disease is defined as 25% increase over the nadir PSA value provided that the increase is at least 5ng/mL and is confirmed. PSA progressions (patients with or without initial decline) must be confirmed at least 4 weeks later.

Duration of PSA Response

Duration of PSA Response is measured from the time when the PSA value first declines by at least 50% of the screening (baseline) and that was eventually confirmed by a second value. It is calculated until the time at which there is an increase of 50% of PSA nadir, provided the absolute increase is at least 5 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 50% above the nadir.

If the PSA never shows a 50% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to Disease Progression

For patients who have achieved a $\geq$ 50% decrease from the screening (baseline) PSA, assessment of time to disease progression is when the PSA has increased 50% above the nadir and at a minimum of 5ng/mL. For patients without a PSA decrease of this magnitude or without a decrease, the time for progression is calculated at the time a 25% increase from screening (baseline) PSA has been achieved.

Appendix 4 Modified Response Evaluation Criteria in Solid Tumors (RECIST)

Quick Reference for the COU-AA-301 study: A Phase 3, Randomized, Double-blind, Placebo Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

Eligibility

- Patients with measurable and non-measurable disease are eligible
- Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Measurable lesions – Visceral or extranodal lesions need to be at least ≥ 10 mm in one dimension using spiral CT; however, lymph nodes need to be ≥ 20 mm in at least one dimension to be considered as target or evaluable lesions to assess changes in size.
- Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm), ie, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment; nodal and visceral/extra-nodal disease will be recorded separately.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤ 5 mm contiguous reconstruction algorithm.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumor lesions.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions.

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for ***all target lesions*** will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of 2 or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair). If 2 or more new bone lesions are the basis for a determination of disease progression, a confirmatory bone scan ≥ 6 weeks later is required that shows ≥ 1 additional new lesion.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Response Criteria

Target lesions	Non-Target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to12 weeks) that is defined in the study protocol
- Disease progression on bone scans will require ≥ 2 new lesions no consistent with tumor flare and must be confirmed on a second bone scan ≥ 6 weeks later that shows ≥ 1 additional new lesion.

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Reporting of Results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.

- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided

Appendix 5 National Cancer Institute Common Terminology Criteria for AEs

V3.0 (CTCAE): publish date August 9, 2006:

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

Appendix 6 ECOG Performance Status

ECOG Grade SCALE

0 Fully active, able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg., light housework, office work.

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 Dead

Appendix 7 Creatinine Clearance

Creatinine clearance (Ccr) is to be estimated by using the following formulas:

$$\text{Adult male Ccr} = \frac{(140 - \text{age}) \times \text{weight measured in kg}}{(72 \times \text{serum creatinine measured in mg/deciliter})}$$

Appendix 8 Brief Fatigue Inventory

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

Appendix 9 Brief Pain Inventory (Short Form)

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

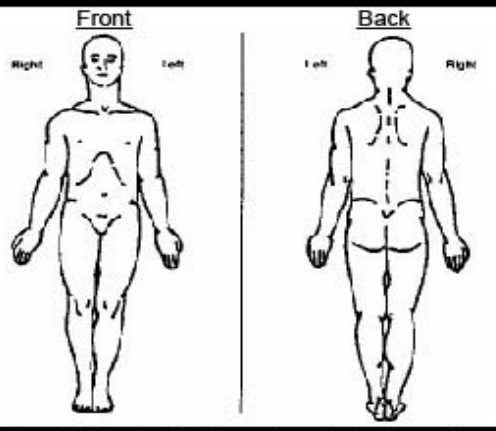
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Page 2 of 2

Appendix 10 Quality of Life

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
GS1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel sad	0	1	2	3	4
GS2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GS3	I am losing hope in the fight against my illness	0	1	2	3	4
GS4	I feel nervous	0	1	2	3	4
GS5	I worry about dying	0	1	2	3	4
GS6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience significant pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BC2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BC5	I am able to have and maintain an erection	0	1	2	3	4

Appendix 11 New York Heart Association (NYHA) Classification

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

http://www.abouthf.org/questions_stages.htm

Appendix 12 Sponsor Signatures

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
Study Number:	COU-AA-301
Protocol Date:	August 26, 2010
Version Number:	4.0

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: Aug 30, 2010

Arturo Molina, MD, MS
Chief Medical Officer
Ortho Biotech Oncology Research & Development,
Unit of Cougar Biotechnology, Inc.

Signed: _____ Date: 30 August 2010

Christopher M. Haqq, MD PhD
Vice President, Clinical Research and Development
Ortho Biotech Oncology Research & Development,
Unit of Cougar Biotechnology, Inc.

Appendix 13 Investigator's Signature

Study Title: A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

Study Number: COU-AA-301

Protocol Date: August 26, 2010

Version Number: 4.0

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>

COUGAR BIOTECHNOLOGY INC.

STATISTICAL ANALYSIS PLAN (SAP) FOR PROTOCOL COU-AA-301

Study Title	A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
Protocol Number	COU-AA-301
Study Phase	3
Product Name	Abiraterone Acetate (CB7630)
IND Number	71,023
EudraCT No	2007-005837-13
Indication	Treatment of Metastatic Castration-Resistant Prostate Cancer
Investigators	Multicenter
Date of Protocol	February 7, 2008
SAP Version	v1.1

Approved by:

Thian Kheoh, Ph.D. — Date

Biostatistician, Cougar Biotechnology, Inc

Arturo Molina M.D., M.S. — Date

Medical Director, Cougar Biotechnology, Inc

Confidentiality Statement

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Abiraterone Acetate (plus prednisone)
AE	Adverse Event
ALB	Albumin
ALK-P	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate aminotransferase
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory-Short Form
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castration-Resistant Prostate Cancer
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DHEA-S	Dihydroepiandrosterone Sulphate
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Ejection Fraction
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FACIT	Functional Assessment of Chronic Illness Therapy
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDH	Lactose Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical Resource Utilization
MUGA	Multiple Gated Acquisition Scan
OS	Overall Survival
PBO	Placebo (plus prednisone)
PK	Pharmacokinetics
PS	Performance Status
PSA	Prostate Specific Antigen
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
R_PFS	Radiographic Progression-Free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
STD	Standard Deviation
T	Serum Testosterone
TLGs	Tables, Listings, and Graphs
TTPAIN	Time to Pain Response
TTPSA	Time to Prostate Specific Antigen Progression
TTSRE	Time to First Skeletal-Related Event
WHO	World Health Organization

1 STUDY DESCRIPTION

1.1 Objectives

The primary objective is to compare the clinical benefit of abiraterone acetate plus prednisone (hereafter called AA) with placebo plus prednisone (hereafter called PBO) in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of which contains docetaxel.

Secondary objectives are as follows:

- To further evaluate the safety profile of abiraterone acetate plus prednisone;
- To further characterize the pharmacokinetics (PK) of abiraterone acetate when administered concurrently with prednisone;
- To further explore the potential utility of circulating tumor cells (CTCs) as a surrogate for clinical benefit;
- To evaluate the impact on quality of life with the administration of abiraterone acetate plus prednisone.

1.2 Study Design

This is a Phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled study with a randomization allocation ratio of 2:1 (AA: PBO). This study will be conducted at approximately 175 investigative sites and approximately 1158 patients will be enrolled. Patients will be stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 versus 2), pain [pain = 4-10 (present) vs pain = 0-3 (absent)], 1 versus 2 prior chemotherapy regimens, and type of progression (PSA only vs. radiographic progression).

Patients in this study will receive abiraterone acetate (1000 mg qd) or placebo (qd). Study treatment (abiraterone acetate or placebo) will be administered along with prednisone (5 mg bid) for both groups. Treatment will continue until clinical or symptomatic disease progression. The study consists of screening, treatment, and follow-up periods.

Within 14 days prior to Cycle 1 Day 1, patients will be screened and evaluated for eligibility for the study.

During the treatment period, patients will return for imaging visits after every 3 cycles until the end of study.

Patient will discontinue from study treatment after all of the following 3 criteria are met:

(1) PSA progression as defined by PSAWG eligibility criteria (25% increase over baseline) with minimum PSA increase of 5 ng/mL;

(2) Radiographic progression defined by ≥1 of the following:

- Soft tissue disease progression by the modified RECIST criteria (baseline lymph node size must be ≥ 2.0 cm to be considered targeted lesion);
- Progression on bone scans with ≥ 2 new lesions not consistent with tumor flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥ 1 additional new lesion;

(3) Symptomatic or clinical progression defined by one of the following:

- Pain progression - Worsening of pain due to metastatic bone disease defined as an increase of ≥ 30% in the worst pain over the past 24 hours on the BPI-SF numeric rating scale observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥ 30% observed at 2 consecutive evaluations 4 weeks apart; to qualify as progression, the BPI-SF score must be ≥ 4;
- Development of a skeletal-related event (SRE) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone;
- Any increase in prednisone or prednisolone or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain are considered a disease progression event;
- Treating physician decides to initiate new systemic anti-cancer therapy.

During the follow-up period, patients will be followed for survival every 3 months up to 60 months, or until lost to follow-up, or withdrawal of informed consent. Survival may be collected by telephone or chart review.

1.3 Sample Size Justification

An overall survival (OS) of approximately 12 months was assumed for this population. Using this as an estimate for the PBO group, a minimal clinically relevant improvement of 25% in the AA group would require a median OS of 15 months; this equates to a hazard ratio (HR) = 0.80. Under these assumptions, and using an exponential distribution for event times, the group sequential testing design described in Section 3.2 would require a maximum of 797 OS events to provide 85% power to detect a 25% improvement in median OS at a 1-tailed significance level of 0.025 (two-tailed alpha of 0.05). Assuming an accrual rate of 89 patients per month with patients randomized in a 2:1 ratio between treatment groups and a total enrollment of approximately 1158 patients, the enrollment would occur over an approximate 13-month period, with approximately 17 months of additional follow up expected in order to observe 797 OS events.

1.4 Method of Assigning Patients to Treatment Groups

Randomization will be performed using a stratified, permuted block design. Strata will be defined according to ECOG (0-1 versus 2), pain (present versus absent), prior chemotherapy (1 versus 2), and type of progression (PSA only versus radiographic progression). All 4 stratification factors listed above represent important prognostic factors that may potentially affect treatment outcome and are included to eliminate bias and to increase the precision of overall treatment effect estimates. The primary analysis on the primary and secondary efficacy endpoints will be based on the stratified logrank test; sensitivity analyses using non-stratified logrank test and Cox proportional hazards model will also be performed as supportive analyses.

Patients will be assigned in a 2:1 ratio to receive either AA or PBO, respectively. The block size will be chosen to minimize the chance of accidental unblinding while sufficiently controlling for potential imbalance between treatment groups, and will be kept confidential as part of the randomization schedule. The randomization schedule will be prepared by an independent statistician not otherwise involved with this study, and will be implemented within a global interactive web response system (IWRS).

1.5 Blinding Procedures

It is the intent for all patients, their families, study team members (at the study site, at Cougar, or at the participating Clinical Research Organization [CRO]), members of the Independent Data Monitoring Committee (IDMC) to remain blinded to treatment group assignment until the completion of the study, with the following exceptions:

- The Independent Biostatistician and Independent Statistical Programmer responsible for preparing interim tables, listings, and graphs for IDMC review. These individuals assigned to this task will be the minimum required, they will have no other responsibilities associated with this study, and they will be restricted from revealing treatment group assignments.
- The IDMC - only if unblinding becomes necessary to fully evaluate whether the study should be stopped early for efficacy/futility or safety. Unblinding procedures and the control of the unblinded data are described in the IDMC charter.
- Laboratory personnel performing blood serum concentration assays for PK analysis and other laboratory tests such as testosterone and dihydroepiandrosterone sulphate (DHEA-S).
- Unblinded safety representative and Ethics Committee for serious adverse event (SAE) reporting except deaths, which is the primary endpoint.

1.6 Protocol and Statistical Analysis Plan (SAP) Amendments

Not applicable at this time

2 STANDARD ANALYSIS CONVENTIONS

2.1 Population Analyzed

The following analysis populations are defined for this study:

- Intent-to-Treat (ITT) Population – all patients randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received. This population will be used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics;
- Safety Population – all patients in the randomized population that receive any part of study drug.

2.2 Study Day and Visit Windows

Patients' time on study will be determined in study days. Study Day 1 will be defined as the day each patient is randomized to the study. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0.

A value obtained on Study Day 1 before administration of study treatment will be considered the baseline value. If a value is not available on Study Day 1, the last available value collected prior to the first dose of study drug will be used as the baseline value.

The study date and corresponding study visit will be captured on each CRF from which study day will be calculated. Visit windows will be created around the study day of each scheduled visit, and will be used to aggregate data for summarization by visit. If more than one assessment falls within the same visit window, then the assessment which occurred first will be used in the analysis. The visit windows and the targeted study day are indicated in Table 1. If an assessment is not scheduled for every visit, windows will be combined so that the interval between targeted study days is split evenly and consistently between visits. Any cycles beyond cycle 12 will have the windows similarly constructed.

Table 1. Visit Windows

Scheduled Study Day	Visit Window		Scheduled Study Day	Visit Window
Baseline	-14, -1		Cycle 6 (Day 140)	127, 154
Day 1*	1, 7		Cycle 7 (Day 168)	155, 182
Day 15	8, 22		Cycle 8 (Day 196)	183, 210
Cycle 2 (Day 28)	23, 42		Cycle 9 (Day 224)	211, 238
Cycle 3 (Day 56)	43, 70		Cycle 10 (Day 252)	239, 266
Cycle 4 (Day 84)	71, 98		Cycle 11 (Day 280)	267, 294
Cycle 5 (Day 112)	99, 126		Cycle 12 (Day 308)	295, 322

* Study Day 1 begins on the day of randomization. Each cycle consists of 28 days

2.3 Missing Data

The following imputation rule will be used for missing data in the assessment of an event:

If only day is missing, missing start day of an event will be replaced by the start day of study treatment if it is the same month and year, otherwise, it will be replaced by the first of the month. If stop day is missing, the stop day of the event will be replaced by the stop day of the end of study treatment or last day of the month and year. Otherwise, the 15th of the month will use to replace the day.

If both day and month are missing, the start day and month will be replaced by the start day and month of study treatment if it occurs in the same year, otherwise, it will be replaced by 1st of January. If the stop day and month are missing, the stop day and month will be replaced by 31st of December. All other cases will be replaced by 1st of July.

3 STATISTICAL ANALYSIS METHODS

All statistical analyses will be performed using SAS®. Given the observed number of events, the adjusted estimates related to the group sequential testing of the primary endpoint will be provided. At the end of the study, summaries and listings will be provided by treatment group for AA and PBO groups. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of patients with a valid measurement (n), mean, standard deviation (STD), median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. Time-to-event endpoints will be analyzed using Kaplan-Meier estimates of survival distributions and the median time-to-event. Inference for time-to-event endpoints will be assessed using a stratified logrank statistic as the primary analysis. The proportional hazard assumption will be assessed graphically by plotting log (-log[estimated survival distribution function]) against log(survival time). The resulting graphs should have approximate parallel lines when the assumption holds. If the proportional hazards assumption is reasonably met, then the HR will be used as an estimate of treatment effect. If the proportional hazards assumption is violated, then the inference remains statistically valid for testing equality in survival distributions, but treatment effect will only be estimated using the median time to event in each treatment group.

3.1 Statistical Hypothesis for the Study Objectives

The primary study objective is to compare the clinical benefit of AA with that of PBO for CRPC patients and will be assessed using OS as the primary endpoint. The hypotheses used to address this objective are as follows:

H_0: The OS distributions of the AA group, $S_A(t)$, and the PBO group, $S_P(t)$, are equal at all time points t:

$S_A(t) = S_P(t)$, for all $t > 0$

versus

Ha: the OS distributions are not equal at least one time point t:

$SA(t) \neq SP(t)$, for some $t > 0$

These hypotheses will be tested using stratified logrank test and assessed within the context of a group sequential testing design as described in Sections 3.2 and 3.3.

3.2 Interim Analysis

Interim analysis will be performed on the primary efficacy endpoint (OS) using the ITT Population; all patients randomized into the study at the time of an interim analysis will be included. One interim analysis and one final analysis are planned after approximately 67% and 100% of the total 797 OS events have occurred. The East® software was used to obtain stopping boundaries that control the overall 1-sided level of significance at alpha 0.025 and provide 85% power to detect a hazard ratio (AA:PBO) of 0.80 (under the assumption of exponentially distributed survival times, a hazard ratio of 0.80 equates to a 25% improvement in median OS for the AA group compared with the PBO group.)

The O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending function were used for the efficacy boundary. Operating characteristics for these boundaries are presented in Table 2, Stopping Boundaries.

Table 2. Stopping Boundaries

	Analyses	
Variable	**Interim**	**Final**
Observed OS Events	534	797
Anticipated Time to Analysis (months)	19	30
Anticipated Enrollment (n)	1158	1158
Efficacy Boundary (HR)	0.7975	0.8628
Cumulative Stop Prob. Under (H_o)	0.0124	0.0500
Cumulative Stop Prob. Under (H_a)	0.4864	0.8500

HR=Hazard ratio; H_o = 0% improvement; H_a = 25% improvement

Analyses are planned following the 534th, and 797th OS events (corresponding to approximately 67% and 100% of the total information); however, the method of constrained stopping boundaries, as implemented in East®, will be used to allow flexibility in the timing of the analyses while controlling the overall 1-sided alpha at 0.025.

The purpose of the interim analyses will be to terminate the study early if superiority of the AA group is demonstrated for the primary endpoint OS. An IDMC will be formed to monitor the safety at regular intervals, and evaluate efficacy at the interim analysis. The decision to terminate the study will be based on a recommendation from the IDMC. The IDMC will be provided with blinded efficacy data at the time of the interim analysis, with the ability to obtain the actual treatment group assignments if this information becomes necessary before recommending that the study be stopped. The IDMC activities and responsibilities are provided in a separate IDMC Charter.

3.3 Analysis Specifications

All hypothesis testing will be performed at a 2-sided significance level of $\alpha = 0.05$. All interval estimation will be reported using 2-sided 95% confidence intervals. Statistical inference on the primary endpoint (OS) will be conducted under group sequential testing design and appropriate adjustment will be provided for multiple testing.

Analyses of all secondary efficacy endpoints will not use group sequential methods, and no adjustments for multiplicity due to repeated testing will be performed for these endpoints. Secondary efficacy endpoints are given in Section 3.5.1, and will be tested using the Hochberg test procedure; ie, testing will begin with p-value $P_{(m)}$ with corresponding hypothesis $H_{(m)}$, where $P_{(m)}$ is the largest ordered p-values amongst 'm' secondary endpoints and $H_{(m)}$ is the corresponding hypothesis. If $P_{(m)} \leq \alpha$, then all hypotheses are rejected. If not, then compare $P_{(m-1)}$ with $\alpha/2$. If smaller, then all hypotheses from $H_{(m-1)}$ to $H_{(1)}$ are rejected. The testing procedure continues in this manner until no significant result is found. This procedure controls the overall level of significance at the 2-sided, 0.05 level.

Descriptive statistics will be reported for all safety data. Inferential statistics are not planned to be performed on safety data, however, selected safety parameters may be statistically analyzed to assist in guiding the review of the data. Further details of the analyses planned for the primary and secondary endpoints are provided in Section 3.5.

3.4 Analysis of Patient Disposition and Treatment

3.4.1 Patient Disposition

Distribution of patients by treatment group for each of the analysis population will be provided. In addition, the number of patients in the ITT Population will be summarized by study site and treatment group.

Treatment discontinuation will be summarized according to reasons of discontinuation (dosing noncompliance, AE, prohibited medications, consent withdrawal, and etc).

3.4.2 Protocol Exemptions and Deviations

3.4.2.1 Protocol Exemptions

In general, patients who do not meet the inclusion/exclusion criteria are not allowed to be entered into the study. However, if exemptions are granted, listings will be provided that include treatment group, patient number, and the criteria being exempted.

3.4.2.2 Protocol Deviations

Protocol deviations will be captured in the Case Report Form (CRF) and review by medical monitor. Protocol deviations will be listed by treatment group, patient number, and categorized according the deviation reasons. If a significant number of deviations occur, a summary table will be produced showing the number of patients for each deviation reasons. Study withdrawal by reasons collected in the CRF (eg, eligibility criteria violation, prohibited concomitant treatment, etc) will also be summarized.

3.4.3 Study Treatment and Extent of Exposure

Treatment compliance will be summarized separately by treatment group at each cycle. Summaries will be reported using descriptive statistics for discrete variables and will be performed using the ITT Population. The summaries will consist of the number and percentage of patients who have completed the specified range of tablets taken, starting at $\leq$ 75% compliance to a maximum of 100% in increments of 5%. Note that in general 120 tablets will be dispensed at each visit cycle, the calculation of the percentages will be the ratio of the number of tablets taken divided by the actual number of days for that visit times 4. In addition, the number of patients completed each cycles will also be presented (regardless of the percent of dose compliance).

Since dose reduction is permitted in the study; the number and percentage of patients with dose reduction will be recorded and summarized according to no dose reduction, 1 dose reduction or 2 dose reductions (2 reductions are the maximum allowed per protocol) at end of study. A patient experiencing dose reduction during the study will be counted according to the highest number of reductions experienced.

3.4.4 Demographics and Baseline Characteristics

Patient baseline demographics and disease status variables will be summarized by treatment group for the ITT Population as described in Table 3.

Table 3. Baseline Demographics and Disease Status	
Variable	**Description**
Baseline Demographics Continuous Variables: • Age (yr) • Weight (kg) • Height (cm) • Body Temperature (^{o}C) • Upright Blood Pressure (mmHg) • Heart Rate (beats/min) • Respiratory Rate (breaths/min) Categorical Variables: • Age group (<65, 65 to 69, 70 to 74, ≥ 75) • Sex (Male) • Ethnicity • Race	(n, mean, STD, median, minimum, and maximum) (n, %)

Baseline Disease Status
Continuous Variables:
• Time from diagnosis
• PSA at diagnosis
• Time since initiating LHRH to study drug
• Time since initiating chemotherapy to study drug
• Baseline Serum PSA
• Baseline pain score
• Baseline analgesic score
• Hgb
• LDH
• Alk Phos
Categorical Variables
• Stage at diagnosis (T, N, M)
• Gleason score (<7, 7 [3+4, 4+3], ≥8)
• Type of progression
  o PSA only
  o Radiographic progression
• Previous cancer treatment (surgery, radiotherapy, hormonal, other)
• Number of prior cytotoxic chemotherapy regimens (1, 2)
• Extent of disease (PSA, prostate, node, bone, visceral, other)
	(n, mean, STD, median, minimum, and maximum)
	
	(n, %)

The distribution of patients within each level of the stratification factors as specified below will also be presented.

1. ECOG PS: 0-1 versus 2

2. Pain: absent versus present

3. Chemotherapy: 1 versus 2

4. Type of progression: PSA only versus radiographic progression

Other than visual inspection, no formal tests to confirm homogeneity between treatment groups at baseline will be performed.

3.4.5 Prior and Concomitant Therapy

For summarization purposes, medications will be coded to a generic term based on the World Health Organization (WHO) dictionary. Medications administered within 30 days prior to the expected first dose will be considered prior medications. Concomitant therapies will be those that are taken on or after Study Day 1 through 30 days post last dose. Incidence of prior medication and concomitant therapies by generic term will be summarized.

3.5 Analysis of Efficacy Endpoints

Analysis of efficacy endpoints will be conducted on the ITT Population.

3.5.1 Efficacy Analysis for the Primary Endpoint

The primary efficacy endpoint is OS defined as the time interval from the date of randomization to the date of death from any cause. Patients alive at time of analysis will be censored on the last date patient was known to be alive or lost to follow-up. The OS distribution and median OS will be estimated using Kaplan-Meier method. Statistical inference will be evaluated in the context of the group sequential testing design described in Section 3.2 and 3.3. The following SAS code will be used in the primary analysis:

```
proc lifetest data=DATASET_NAME;
        time OSTIME*CENSOR(0);
        strata ECOG_CAT PAIN_CAT CHEM_CAT PROG_CAT /
        group=TREATMENT;
        run;
```

where DATASET_NAME is the name of the dataset, OSTIME is a vector containing the OS measurement for each patient, CENSOR is its respective censoring vector, TREATMENT is a vector containing treatment group assignment, ECOG_CAT is a vector containing the ECOG performance status category, PAIN_CAT is a vector containing the pain category, CHEM_CAT is a vector containing the number of prior chemotherapy category, and PROG_CAT is a vector containing the type of progression category.

The resulting statistic (stratified logrank test statistic) will be evaluated using East® to ensure that it is compared to the appropriate stopping boundary given the precise number of events observed at the time of the interim analysis. If the statistic crosses a stopping boundary, then the p-value from the SAS output will be used.

Supportive analysis using the Cox proportional hazards model using the following SAS code will also be performed.

```
proc phreg data=DATASET_NAME;
  model OSTIME*CENSOR(0)=TREATMENT / ties=discrete;
  strata ECOG_CAT PAIN_CAT CHEM_CAT PROG_CAT;
  run;
```

where the variable names are as defined above. The score statistic (which is equivalent to logrank test statistic) may be used to provide an adjusted estimate of the HR and corresponding 2-sided 95% confidence interval. This information will be included in the IDMC package for review as detailed in the IDMC charter and interim analysis plan.

3.5.1 Efficacy Analyses for the Secondary Endpoints and Other Endpoints

Secondary endpoints are defined and listed in Table 4. Comparisons between treatment groups will be conducted according the Hochberg's test procedure as described in Section 3.3.

Table 4. Secondary Endpoints

Variable	Description
PSA_RESP	PSA Response Rate Proportion of patients achieving a PSA decline of at least 50% according to protocol specific PSAWG criteria.
TTPSA	Time to PSA Progression The time interval from the date of randomization to the date of the PSA progression as defined in the protocol specific PSAWG criteria (Appendix 3 of protocol). Other note: • Patient must have received at least 3 cycles of therapy to be considered a PSA progressor; a rise in PSA alone, in the absence of radiographic progression, during the first 3 cycles will not be considered disease progression
R_PFS	Radiographic Progression-Free Survival Progression-Free survival based on imaging studies. The time interval from the date of randomization to the date of the event as assessed by the investigator (i.e., radiographic disease progression or death) Radiographic progression is defined as: • Soft tissue disease progression by modified RECIST criteria (baseline lymph node size must be ≥2.0 cm to be considered target lesion), or • Progression on bone scans with ≥2 new lesions not consistent with tumor flare, confirmed on a second scan ≥6 weeks later that shows ≥1 additional new lesion. Other note: • Non-target abnormality will be recorded as present at baseline followed-by present/absent or increased/decreased • If no event exists, then PFS will be censored at the last scheduled disease assessment on study. PFS of living patients with no assessment on-study, and PFS of patients with no baseline assessment will be censored at randomization.

Other endpoints to be analyzed are included in Table 5. No adjustments for multiple testing are planned; each comparison between treatment groups will be carried out at alpha 0.05.

Table 5. Other Endpoints

OR	Objective response rate A patient achieving a complete or partial response according to modified RECIST criteria (baseline lymph node size must be ≥2cm to be considered targeted lesion)
PAINRESP	Pain Palliation Rate Proportion of patients experiencing pain palliation. A patient is a responder if the patient experiencing a reduction of ≥30% in the BPI-SF worst pain intensity score over the last 24 hours observed at 2 consecutive evaluations 4 weeks apart without any increase in analgesic usage score (ie, best response). Other note: • Only patients experiencing pain score ≥4 at baseline will be included in the calculation.
TTPAIN	Time to Pain Progression The time interval from the date of randomization to the first observation of symptomatic pain progression. Pain progression is defined as follows: BPI-SF increase by ≥30% in the BPI-SF worst pain intensity score over the last 24 hours observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or Increase in analgesic usage score ≥30% observed at 2 consecutive evaluation 4 weeks apart Other note: • Only patients experiencing pain score ≥4 at baseline will be included in the calculation.
TTSRE	Time to First Skeletal-Related Event The time interval from the date of randomization to the first observation of skeletal-related event. Skeletal-related event is measured by the time to pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone Other note: • In the absence of skeletal-related events, events will be censored at the last assessment in the study. Patients with no such assessment on-study will be censored at randomization.

Table 5. Other Endpoints (Cont'd)

M_PFS	Modified PFS Modified PFS based on criteria for discontinuation of study treatment. The time interval from the date of randomization to death or the first observation of the following: 1) PSA progression, and 2) Radiographic progression, 3) Increase in glucocorticoid use, and 4) Pain progression or SRE or physician decides to initiate new systemic anti-cancer therapy. Other notes: • See treatment discontinuation criteria in protocol. • If physician decides to initiate new therapy, the date of the decision will be used for the event.
CTC_RESP	CTC Response Rate Proportion of patients achieving a decline in circulating tumor cells (CTCs/7.5ml) to < 5. A patient is a responder if the patient's baseline CTC≥5 followed-by the post-baseline CTC<5 at any visit (ie, best response)
QOL	Total score and each subscale score from FACT-P (physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer subscale)

Table 6 provides censoring rules for time-to-event endpoints (except for OS).

Table 6. Censoring Rules for Time-To-Event Endpoints (Except OS)

Situation	Date of Censoring	Endpoints
No baseline assessment	Randomization	ALL
Lost to follow-up before event	Date of last visit	ALL
New cancer therapy	Date of last visit	ALL
Study noncompliance	Date of last visit	ALL
Death (any cause)	Date of death	TTPSA, TTPAIN, TTSRE

Time-to-event endpoints will be analyzed using Kaplan-Meier estimates of survival distributions and median survival times. Statistical inference will be evaluated similarly as in the primary analysis using the score test from a stratified Cox proportional hazard model, except that they will not be evaluated using the group sequential testing design. Response endpoints (PSA response rate, CTC response rate, pain palliation rate, and objective response rate) will be summarized using descriptive statistics for categorical data by dose group. The relative risk (treatment:control) will be reported along with the associated 2-sided 95% confidence intervals. Statistical inference will be evaluated using the Chi-square statistic; the Fisher's exact test may be used if the expected counts in some cells are small. The SAS® code of the following form will be used:

```
proc freq data=ANALYSISFILE order=formatted;
   tables TREATMENT*RESPONSE / chisq relrisk;
run;
```

where ANALYSISFILE is the analysis file containing the objective response measurements, TREATMENT is the variable containing treatment group assignment, and RESPONSE is the variable containing the indicator for response.

Secondary efficacy endpoints will not be evaluated using the group sequential testing design, and p-values will not be adjusted for interim analyses. However, the Hochberg's test procedure will be implemented as described in Section 3.3 will be used to control for multiple comparisons and ensure an overall 2-sided level of significance of 0.05.

Other efficacy endpoints will be analyzed but no adjustments for multiplicity are planned. Comparisons will be tested at alpha 0.05 for each of the endpoint.

3.5.2 Sensitivity Analysis and Subgroup Analysis

Sensitivity analyses on primary and secondary endpoints will be performed to assess the robustness and consistency of the endpoints. The results from the analyses will not be adjusted for multiplicity testing. Each analysis will be compared at significance level of 0.05.

3.5.2.1 Sensitivity Analysis and Subgroup Analysis for the Primary Endpoint

The non-stratified analysis on primary endpoint of OS will be performed. Since this analysis is not being analyzed in the context of group sequential testing design, no adjustment will be made to the p-values or estimated treatment effects. The modeling will be performed using SAS® code of the following form:

```
Proc phreg data=ANALYSISFILE;
   Model OSTIME*CENSOR(0) = TREATMENT;
    run;
```

where OSTIME, CENSOR, and TREATMENT are as defined above. Statistical significance will be assessed using the score statistic (which is equivalent to a logrank test).

Subgroup analysis is planned for the primary endpoint (OS) to investigate whether treatment effects are consistent within subgroups. Each subgroup will be analyzed separately. The subgroups are as follows:

1. Patients whose baseline PSA is greater than the median baseline value
2. Patients whose PSA value drops at least 30% from baseline value
3. Patients who entered the study with PSA progression alone
4. Patients who entered the study with radiographic progression
5. Patients who entered the study with visceral disease
6. Patients whose LDH value is greater than the median baseline value
7. Patients whose ALK-P value is greater than the median baseline value
8. Patients who are considered a CTC responder
9. Region (North America vs non-North America)

The hazard ratio within each subgroup will be estimated using a Cox proportional hazard non-stratified model. Results from these analyses will not be considered inconsistent with the primary analysis unless the 95% confidence interval for the hazard ratio within a subgroup does not include the point estimate for the primary analysis.

Additional analyses may be performed if appropriate.

3.5.2.2 Sensitivity Activity for Secondary Endpoints and Other Endpoints

Sensitivity Analysis for Pain Endpoints

Additional analyses for the pain associated endpoints will be performed:

(a) The pain palliation rate (PAINRESP) and time to pain progression (TTPAIN) will be analyzed for patients who experience any level of pain at baseline using the same method of analysis as described in Section 3.5.1.

(b) The pain palliation rate will be summarized for the percent of pain reduction, in increment of 10%.

3.6 Analysis of Safety Endpoints

The safety variables to be analyzed include AEs, ECGs, MUGA/ECHO, routine hematology CBC with differential and platelet count, coagulation factors, serum chemistry panel, serum lipids, vital sign measurements, and deaths. Unless otherwise noted, safety variables will be tabulated by descriptive statistics (n, mean, median, STD, minimum, and maximum; or n and percent) using the Safety Population.

3.6.1 Clinical Adverse Events

Adverse events are coded to System Organ Class and preferred terms using the MedDRA® coding system (version 8.1 or higher).

The severity of AEs will be graded on a scale of 1 to 5 according to the adult NCI Common Terminology Criteria for Adverse Events (CTCAE version 3.0) where higher grades indicate events of higher severity. Adverse events will be summarized by grade according to the worst grade experienced.

Table 7 describes the summaries of AEs that will be provided as incidence tables (number of patients experiencing an event) by treatment group and overall. For summary purposes, AEs will be defined as all reported events with a start date on or after Study Day 1 or that increase in severity on or after Study Day 1. All AEs are collected through 30 days post last dose.

All AEs will have their relationship to study drug evaluated as unrelated, unlikely, possibly, or related. Adverse events will be categorized and summarized according to their highest relationship to study drug. Adverse events reported as possibly related or related will be classified as treatment-related AEs.

Table 7. Summary of Adverse Events and Treatment-Related

Summary	Sorted By	All Study Events	Treatment-Related Events
AEs	System organ class, preferred term		✔
	System organ class, preferred term, grade	✔	
Most common (≥ 5%) AEs	System organ class, preferred term	✔	
Grade 3, 4, or 5 AEs	System organ class, preferred term	✔	✔

Listings will be provided for patients who experienced any Grade 3, 4, or 5 AEs.

3.6.2 Clinical Laboratory Test Analyses

3.6.2.1 Hematology Results

The hematology values to be measured include hemoglobin, hematocrit, platelet counts, red blood cells, white blood cells and absolute neutrophil count. Mean change will be summarized at scheduled visits and, for selected variables, will be presented in figures showing the change in values over time. Shift table analyses for select hematology variables (hemoglobin, hematocrit, platelets, white blood cells, and neutrophils) are to be performed summarizing the number of patients with shift outside the normal ranges between baseline and maximum (and minimum) values observed post-baseline. A listing of patients who experienced a shift to outside the normal ranges will be presented.

Nadir analyses will be performed for selected variables (as in shift table above), summarizing the following information: baseline value, nadir value, number and percent of patients, number of days from baseline to nadir, and the number of days from nadir to recovery.

In addition, coagulation factors will also be summarized using descriptive statistics at baseline.

3.6.2.2 Blood Chemistry Results

The blood chemistry values to be measured include albumin (ALB), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, cholesterol, HDL, LDL, triglyceride, lactose dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Mean values will be summarized at scheduled visits and, for select variables in potassium, calcium, AST, ALT, total bilirubin, ALK-P, cholesterol, HDL, and LDL will be presented graphically showing the change in values over time. Shift table analyses for select chemistry variables (as above) are to be performed summarizing the number of patients with shift outside the normal ranges between

baseline and maximum (and minimum) values observed post-baseline. A listing of patients who experience a shift to outside the ranges will be presented.

3.6.2.3 Urinalysis

Serum lipids will be collected at baseline and during treatment. Mean change in serum lipids will by provided by visits.

3.6.2.4 Urinalysis

Urinalysis data is collected at baseline. Results will be summarized using descriptive statistics of categorical data as well as continuous data.

3.6.3 Additional Laboratory Tests

The additional laboratory tests include PSA, serum testosterone (T), and other androgens such as DHEA-S. These variables will be summarized similarly to blood chemistry results.

3.6.4 Vital Signs

Vital sign measurements collected will include blood pressure, heart rate, respirations, and body temperature. Body temperature will be collected in °F or °C, but reported in °C. Data will be converted to °C for summarization purposes using the following formula: °C = 5/9 (°F – 32).

Vital signs and change from baseline in vital signs will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) at each scheduled visit.

3.6.5 Premature Discontinuations due to Adverse Events

A summary of reasons for discontinuation will be provided summarizing the number and percentage of patients for each reason. A listing of premature discontinuations due to AEs including the patient number, site, treatment group, start date and study day of AE, severity, relationship to study regimen, action taken, and outcome of AE will be provided. Additional summary table summarizing preferred term may be provided if warranted.

3.6.6 Serious Adverse Events (SAE)

A listing of SAEs including the patient number, site, treatment group, start date and study day of SAE, severity, relationship to study drug, action taken, and outcome of SAE will be provided. Additional summary table by preferred term may be provided if warranted.

3.6.7 Deaths

A listing of deaths including the patient number, site, treatment group, date and study day of death, and cause of death will be provided.

3.6.8 Electrocardiograms (ECGs)

Descriptive statistics for the QTc, PR interval, and QRS at each study visit will be presented. Summary tables comparing baseline and maximum on-study QTc change will be provided. Paired-t tests will be computed with p-values provided as a guide in the interpretation of the results only and not for inferential purposes. No adjustment to account for multiple testing is planned. Patients whose QTc increases > 60msec, or who have QTc > 500msec on study will be listed. For all tables and summaries, both the Fredericia and Bazett corrections will be reported. The QTc calculations will be corrected according to the ventricular rate.

3.6.9 Multiple Gated Acquisition (MUGA) /Echocardiogram (ECHO) Scan

Distribution of the results from MUGA and/or ECHO will be summarized in increment of 10% by the number and percentage of patients whose ejection fraction (EF) drops below 50%. Patients experiencing EF<50% will be listed.

3.7 Pharmacokinetics

Approximately 150-200 patients are scheduled to be enrolled at selected sites for the PK sub-study. Based on the 2:1 randomization this should yield approximately 100-150 patients on active treatment (abiraterone acetate).

Nonlinear mixed effects modeling will be used to develop a population PK model for abiraterone plasma concentrations in HRPC patients. A covariate analysis will be performed to investigate the influence of patient factors on the apparent clearance of abiraterone. Patient factors will include, but are not limited to, body weight, calculated creatinine clearance, liver function, sex, age, race, and time of meal relative to the time of dose administration. Patient factors on other disposition and absorption parameters will be tested in a secondary fashion. A separate report will be presented summarizing the results from the modeling.

3.8 Circulating Tumor Cells (CTC)

The change in CTC counts will be descriptively summarized. Analysis methods for proportion of CTC responder and its potential clinical benefit with respect to the primary endpoint are described in Sections 3.5.1 and 3.5.2. Analyses on CTC responders will also be presented by visit. Additional analyses to explore CTC enumeration as surrogate for clinical benefit will be provided in a separate report.

3.9 Analysis of Quality of Life and Other Outcome Measurements

3.9.1 Quality of Life (QOL)

Quality of Life (QOL) assessments will be performed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire, version 4. Scoring guidelines for the FACT-P, as well as handling of missing data will be in accordance with methodology described in the Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, version 4.0 (November 1997). Quality of Life assessments will be performed prior to treatment, following the treatment regimen at cycles 1, 4, 7, 10, and end of study. Descriptive statistics will be presented for each item collected for QOL. The FACT-P subscale scores (eg, physical, social/family, emotional, functional well-being, and additional concerns) and total score will be summarized descriptively by scheduled visit. Statistical analysis using paired t-test will be carried out to compare between during treatment visit score with baseline score. Repeated measures analysis may also be employed as appropriate.

Analysis of pharmacoeconomic data (including Medical Resource Utilization, MRU) will be summarized and presented in a separate report.

3.9.2 Brief Fatigue Inventory

Brief Fatigue Inventory (BFI) data will be collected at all scheduled visits and will be descriptively summarized by visit.

3.9.3 Brief Pain Inventory

Brief Pain Inventory - Short Form (BPI-SF) will be collected at all scheduled visits. Descriptive statistics for each items collected (where appropriate) will be presented by visits. Graphical displays showing change over time will be provided for each item.

4 LIST OF PLANNED TABLES AND FIGURES

4.1 Clinical Study Report (CSR) In-Text Tables

1. Distribution of Patients by Analysis Population
2. Number of Patients in the Intent-to-Treat Population by Country and Study Site
3. Number of Cycles Completed During Study
4. Reasons for Study Withdrawal
5. Patient Distribution by Stratification Factors
6. Demographics
7. Baseline Disease Status
8. Prior Therapies
9. Concomitant Medications
10. Treatment Compliance
11. Dose Reduction by Treatment Group
12. Primary Endpoint: Overall Survival
13. Summary of Secondary Endpoints: Time-to-Event Endpoints
14. Summary of Secondary Endpoints: Response Endpoints
15. Summary of Other Endpoints: Time-to-Event Endpoints
16. Summary of Other Endpoints: Response Endpoints
17. Incidence of Most Common (≥5%) Adverse Events by System Organ Class and Preferred Term
18. Incidence of All Grade 3, 4, and 5 Adverse Events by System Organ Class and Preferred Term
19. Listing of Treatment Discontinuation Due to Adverse Events
20. Shift Table Analyses of Select Hematology Variables
21. Shift Table Analyses of Select Serum Chemistry Variables
22. Listing of Serious Adverse Events
23. Listing of Patient Deaths
24. ECOG Performance Status

4.2 Clinical Study Report (CSR) In-Text Figures

1. Kaplan-Meier Curves for Overall Survival
2. Kaplan-Meier Curves for Progression-Free Survival
3. Kaplan-Meier Curves for Time to Pain Progression
4. Kaplan-Meier Curves for Time to Skeletal-Related Events
5. Mean Hematology Variables Over Time (Select Variables)
6. Mean Serum Chemistry Variables Over Time (Select Variables)
7. Mean BPI Item Score Over Time

4.3 Clinical Study Report (CSR) Appendix Tables

1. Listing of Abiraterone Acetate Lot Numbers by Patient and by Study Site
2. Listing of Protocol Exemptions (if applicable)
3. Listing of Protocol Deviations
4. Summary of Protocol Deviations Reasons (if applicable)
5. Mean Change in Vital Signs Over Time
6. Sensitivity Analysis for Overall Survival
7. Subgroup Analyses for Overall Survival
8. Incidence of Adverse Events by System Organ Class, Preferred Term, and Grade (Overall)
9. Incidence of Study-Related Adverse Events by System Organ Class and Preferred Term (Overall)
10. Incidence of All Grade 3, 4, and 5 Study Related Adverse Events by System Organ Class and Preferred Term (Overall)
11. Listing of Grade 3, 4, and 5 Adverse Events
12. Mean Change in Hematology Over Time
13. Nadir Analysis – Hematology
14. Summary of Coagulation Factors
15. Listing of Patients Shift Outdside the Normal Range for Select Hematology Variables
16. Mean Change in Serum Chemistry Over Time
17. Nadir Analysis – Chemistry
18. Listing of Patients Shift Outside the Normal Range for Select Chemistry Variables
19. Mean Change in Serum Lipids
20. Urinalysis

21. ECG
22. Summary of QTc Results
23. Listing of Patients with Change from Baseline QTc>60msec or Actual QTc>500msec (if applicable)
24. ECHO/MUGA Results
25. Listing of Patients with EF<50% (if applicable)
26. CTC Response Analysis
27. FACT-P: Physical Well-Being
28. FACT-P: Social/Family Well-Being
29. FACT-P: Emotional Well-Being
30. FACT-P: Functional Well-Being
31. FACT-P: Overall
32. BFI Inventory Score Over Time
33. BPI Inventory Score Over Time
34. FACT-P: Prostate Cancer Subscale
35. Incidence of Study-Related Adverse Events by System Organ Class, Preferred Term Attributed to Arbiraterone Acetate/Placebo
36. Incidence of Study-Related Adverse Events by System Organ Class, Preferred Term Attributed to Prednisone/Placebo